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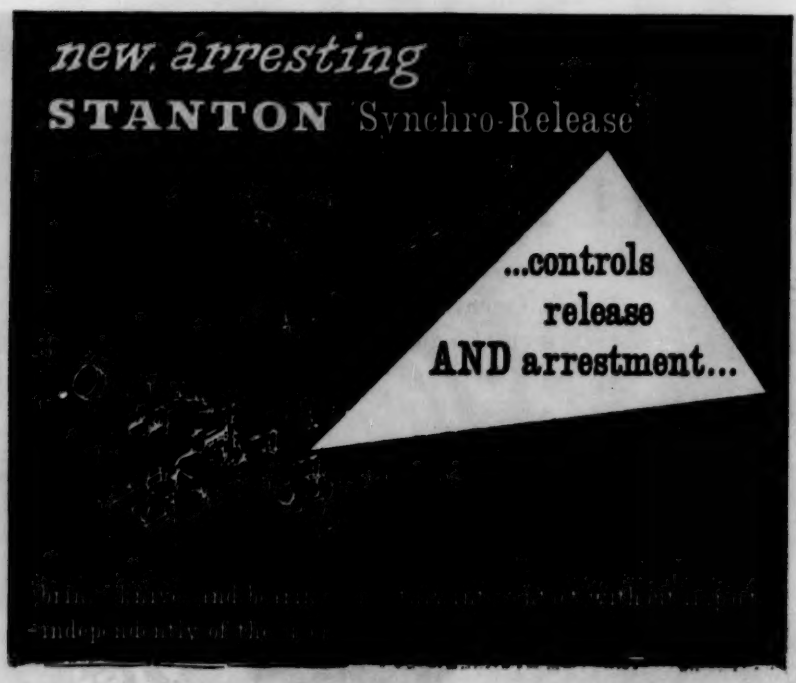

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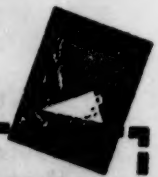

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The Alkaline Fission of 2-Aroyloxyethyldimethylsulphonium Iodides: The Evaluation of Hammett's Substituent Constants for some ortho-*Substituents.*

By P. Mamalis and H. N. Rydon.

[Reprint Order No. 5875.]

It is shown that the ready alkaline fission of 2-aroyloxyethyldimethylsulphonium iodides (Crane and Rydon, *J.*, 1947, 766) proceeds in two stages:

$$\underset{\text{(I)}}{Ar\cdot CO_2\cdot CH_2\cdot CH_2\cdot \overset{+}{S}Me_2\}I^-} + NaOH \rightleftharpoons Ar\cdot CO_2Na + \underset{\text{(II)}}{CH_2{:}CH\cdot \overset{+}{S}Me_2\}I^-} + H_2O \quad \text{(i)}$$

$$CH_2{:}CH\cdot \overset{+}{S}Me_2\}I^- + NaOH \longrightarrow CH{:}CH + SMe_2 + NaI + H_2O \quad \text{(ii)}$$

only the first of which occurs at room temperature, the second requiring heating to 95°.

The rates of alkaline fission at 25° of thirteen sulphonium iodides (I) have been determined. Consideration of the results and of the conditions under which dimethylvinylsulphonium iodide (II), 2-hydroxyethyldimethylsulphonium iodide, and bis-2-methylthioethyl ether bismethiodide are formed from (I) leads to the conclusion that the elimination reaction (i) is reversible, the double bond of (II) being so activated by the adjacent sulphonium pole as readily to undergo additive attack by anions. The mechanisms of the various reactions are discussed.

Hammett substituent constants, σ, are evaluated for *o*-nitro-, *o*-chloro-, *o*-methyl, and *o*-methoxyl groups.

Crane and Rydon (*J.*, **1947**, 766) showed that 2-benzoyloxyethyldimethylsulphonium iodide, $Ph\cdot CO\cdot O\cdot CH_2\cdot CH_2\cdot \overset{+}{S}Me_2\}I^-$, was remarkably sensitive to alkali, consuming alkali in the cold and breaking down in warm alkali to yield benzoic acid, acetylene, and dimethyl sulphide. The work described in the present paper was undertaken with the object of elucidating the mechanism of this reaction, primarily by studying the influence of substituents in the aroyl group on its rate.

Thirteen 2-aroyloxyethyldimethylsulphonium iodides (I; R = H; *o*-, *m*-, *p*-NO_2; *o*-, *m*-, *p*-Cl; *o*-, *m*-, *p*-Me; *o*-, *m*-, *p*-MeO) were prepared by the action of methyl iodide

$$\text{(I)}\quad R\cdot C_6H_4\cdot CO\cdot O\cdot CH_2\cdot CH_2\cdot \overset{+}{S}Me_2\}I^-$$

on the corresponding 2-aroyloxyethyl methyl sulphides, obtained by aroylation of 2-hydroxyethyl methyl sulphide in pyridine; some of the iodides were converted into the corresponding chlorides by double decomposition with silver chloride. Some homologues of (I), *viz.*, 3-benzoyloxypropyl-, 3-*p*-nitrobenzoyloxypropyl-, and 4-benzoyloxybutyl-dimethylsulphonium iodides, were prepared similarly; 2-benzoyloxyethyl methyl sulphoxide and sulphone, and 2-*p*-nitrobenzoyloxyethyl methyl sulphone were prepared by oxidation of the corresponding sulphides. The preparations of several other sulphides and derived sulphonium iodides and sulphones are recorded in the Experimental section.

Experiment soon showed that Crane and Rydon (*loc. cit.*) were mistaken in supposing the decomposition of 2-benzoyloxyethyldimethylsulphonium iodide to proceed in one stage in the cold, thus:

$$Ph\cdot CO_2\cdot CH_2\cdot CH_2\cdot \overset{+}{S}Me_2\}I^- + 2NaOH \longrightarrow Ph\cdot CO_2Na + CH{:}CH + SMe_2 + NaI + 2H_2O$$

In the cold, at pH *ca.* 10, only one equivalent of alkali is consumed, the major reaction being elimination of benzoic acid, thus:

$$Ph\cdot CO_2\cdot CH_2\cdot CH_2\cdot \overset{+}{S}Me_2\}I^- + NaOH \longrightarrow Ph\cdot CO_2Na + \underset{\text{(II)}}{CH_2{:}CH\cdot \overset{+}{S}Me_2\}I^-} + H_2O \quad \text{(i)}$$

Acidification at this stage gave an almost theoretical yield of benzoic acid; the formation of dimethylvinylsulphonium iodide (II) in 70% yield was established by addition of sodium

picrylsulphonate (Stahmann, Fruton, and Bergmann, *J. Org. Chem.*, 1946, **11**, 518, 704), which resulted in the precipitation of the beautifully crystalline dimethylvinylsulphonium picrylsulphonate. The identity of the latter compound was established by mixed m. p. with a specimen prepared by the action of aqueous sodium hydrogen carbonate on 2-chloroethyldimethylsulphonium iodide, followed by conversion of the resulting dimethylvinylsulphonium iodide (II) into the picrysulphonate. The elimination reaction (i) was accompanied, to a small extent, by substitution:

$$Ph{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^- + NaOH \longrightarrow Ph{\cdot}CO_2Na + HO{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^-$$
(III)

the formation of 2-hydroxyethyldimethylsulphonium iodide (III) being established by the isolation of a small amount of the derived picrylsulphonate, identified by mixed m. p. with material prepared from (III) obtained by the action of methyl iodide on 2-hydroxyethyl methyl sulphide. A second equivalent of alkali was consumed by 2-benzoyloxyethyldimethylsulphonium iodide only at 95°; under these conditions the dimethylvinylsulphonium iodide (II), formed in the first stage, broke down thus:

$$CH_2{:}CH{\cdot}\overset{+}{S}Me_2\}I^- + NaOH \longrightarrow CH{\vdots}CH + SMe_2 + NaI + H_2O \quad . \quad . \quad . \quad (ii)$$

Dimethyl sulphide was identified as its mercurichloride (50% yield), and acetylene by the formation of cuprous acetylide with the cuprous chloride–hydroxylamine reagent. A similar two-stage reaction was established in the same manner for the *m*-nitro- and the *o*-methyl compound (I; R = *m*-NO_2 and *o*-Me).

The ready elimination reaction (i) was studied kinetically, for the thirteen 2-aroyloxyethyldimethylsulphonium iodides (I) in aqueous solution at 25°, by continuous titration at various pH values, using the very convenient apparatus of Powell and Trendall (*Chem. and Ind.*, 1943, **62**, 368); the reactions were followed only up to 50% reaction, at which stage they were becoming inconveniently slow. The reaction is of the second order, being closely of first order with respect to both sulphonium and hydroxyl ions. The results are given in full in Table 3, while the values of the second-order velocity constant, k_2, are collected in Table 1. It will be seen that the reaction is facilitated by electron-attracting substituents, and hindered by electron-releasing substituents, in the phenyl group and that there is no obvious *ortho*-effect.

TABLE 1. *Second-order velocity constants (l. mole^{-1} min.$^{-1}$) for alkaline fission of*

$$R{\cdot}C_6H_4{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^- \text{ at } 25°.$$

R Concn. (M):	0·002	0·005	0·0075	0·01	R Concn. (M):	0·002	0·005	0·0075	0·01
H	—	356·5	322·1	284·4	*m*-Cl	—	543·3	—	492·0
		(321·4 *)		(294·4 *)	*p*-Cl	512·9	476·4	—	—
o-NO_2	—	1242	—	1164	*o*-Me	—	314·1	—	243·8
				(1148 †)	*m*-Me	—	322·1	—	272·3
m-NO_2	—	1285	—	1086	*p*-Me	—	319·2	—	244·9
p-NO_2	2061	1611	1607	1358	*o*-MeO	—	291·1	—	266·7
				(1524 †)	*m*-MeO	—	372·4	—	261·2
o-Cl	—	673·0	—	595·7	*p*-MeO	—	212·8	—	178·2

* Chloride. † 0·005M-Sulphonium iodide + 0·005M-KI.

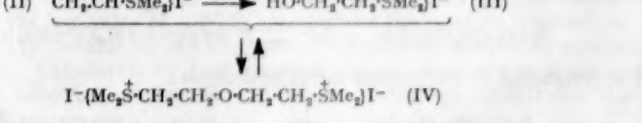
As expected for a reaction between a positive and a negative ion, the reaction shows a negative primary salt effect; this is demonstrated both by the decrease in k_2 with increasing sulphonium iodide concentration and by the similar retardation of the reaction brought about by the addition of potassium iodide. The slope of the plot of log k_2 against $\sqrt{\mu}$, where μ is the mean ionic strength, is not −1, as required by the simple Brønsted–Bjerrum theory (Brønsted, *Z. physikal. Chem.*, 1922, **102**, 169; Bjerrum, *ibid.*, 1924, **108**, 82), but is steeper than this; this is not unexpected with an ion, such as the cation of (I), which is far from spherical (cf. Olson and Simonson, *J. Chem. Phys.*, 1949, **17**, 1167).

Dimethyl-3-*p*-nitrobenzoyloxypropylsulphonium iodide reacts with alkali more slowly

than its lower homologue (I; R = *p*-NO_2), k_2 being 367·3 for 0·005M initial concentration and 328·1 for 0·01M. 2-Benzoyloxyethyl methyl sulphone was observed to react at about the same rate as the sulphonium iodide (I; R = H), but full kinetic experiments were not carried out; the corresponding sulphoxide reacted immeasurably slowly, as also did 2-benzoyloxyethyltrimethylammonium iodide.

In view of the qualitative observation that, in the unsubstituted case (I; R = H), elimination was accompanied by a small amount of substitution, it seemed necessary to determine the proportions in which the vinyl (II) and hydroxyethyl (III) compounds were formed from the various iodides (I), under the conditions obtaining in the kinetic experiments. Accordingly the thirteen iodies (I) in 0·005M- and 0·01M-solution were titrated with N-sodium hydroxide (1 equivalent); the vinyl- and 2-hydroxyethyl-sulphonium iodides (II) and (III) formed were then estimated by conversion into the picrylsulphonates and fractional crystallisation. The results, for which no great accuracy is claimed, are given in Table 4; it will be seen that there is a correlation with the electronic effect of R, electron-attracting substituents favouring the formation of the hydroxyethyl compound (III), and that there is a marked *ortho*-effect, the proportion of (III) formed from each of the three *o*-compounds being notably smaller than that from the corresponding *m*- and *p*-compounds. Under similar conditions, but in more concentrated solution, dimethyl-3-*p*-nitrobenzoyloxypropylsulphonium iodide gave only 3-hydroxypropyldimethylsulphonium iodide, the homologue of (III). Titration of 2-benzoyloxyethyldimethylsulphonium iodide (I; R = H) in 0·5M-solution in methanol, with sodium methoxide, gave only 2-methoxyethyldimethylsulphonium iodide, $MeO{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^-$.

Owing to the difficulty of controlling pH closely in these large-scale titrations, it was thought desirable to investigate the effect of higher pH; this was done, in the case of the unsubstituted compound (I; R = H), only, by treating the iodide with sodium hydroxide added in one portion, keeping the mixture overnight, and then isolating the sulphonium compounds present as their picrylsulphonates. This reaction was found to be very sensitive to small amounts of alkali in excess of one equivalent; the results of a series of experiments in which 1·00—1·24 equivalents of alkali were used are shown in Table 5. With exactly one equivalent of alkali, the vinyl (II) and hydroxyethyl (III) compounds are the only products but the use of more than one equivalent of alkali leads to the formation of a third sulphonium compound, characterised by a very insoluble picrylsulphonate. This third sulphonium compound proved to be bis-2-methylthioethyl ether bismethiodide (IV); this identity was established by comparison of the bismethiodide itself, as well as the derived chloride, picrate, and picrylsulphonate, with the compound synthesised from bis-2-methylthioethyl ether, prepared by methylation of bis-2-mercaptoethyl ether. The results summarised in Table 5 show that the ether (IV) is formed at the expense of the vinyl compound (II), rather than at the expense of the hydroxyethyl compound (III). Further experiments showed that the vinyl compound (II) was converted into the ether (IV) in weak alkali (*ca.* 0·02N) overnight in the presence of benzoate anions and that both (II) and (IV) were converted into (III) if kept overnight with stronger alkali (*ca.* 0·2N). The relations of the three sulphonium compounds are expressed in the following reaction scheme:



It is clear from these findings that the hydroxyethyl compound (III) isolated in the large-scale titration experiments cannot have arisen by direct addition of water to the vinyl compound (II), since this reaction has been demonstrated to require much more strongly alkaline conditions.

In other experiments, which were carried out before the sensitivity of the reaction to a slight excess of alkali was realised and in which a slight excess may well have been used, treatment of the *o*-, *m*-, and *p*-nitro- and *p*-chloro-compounds (I; R = *o*-, *m*-,

p-NO_2, and *p*-Cl) with approximately one equivalent of alkali, added in one portion, gave the ether (IV) in 16%, 32%, 34%, and 67% yield, respectively. The ether (IV) was similarly obtained from dimethyl-2-phenoxyethylsulphonium iodide. 2-Benzoyloxyethyl methyl sulphone afforded the analogous bis-2-methylsulphonylethyl ether, $Me{\cdot}SO_2{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}SO_2{\cdot}Me$, under similar conditions whereas 2-benzoyloxyethyl methyl sulphoxide was unaffected. Two higher homologues of (I), *viz.*, dimethyl-3-*p*-nitrobenzoyloxypropylsulphonium iodide and 4-benzoyloxybutyldimethylsulphonium iodide, afforded the corresponding hydroxy-compounds, homologues of (III); the choline derivatives, 2-benzoyloxyethyl- and 2-*p*-nitrobenzoyloxyethyl-trimethylammonium iodide, likewise yielded only 2-hydroxyethyltrimethylammonium iodide.

Having thus demonstrated that, under the conditions of the kinetic experiments, the hydroxyethyl compound (III) cannot arise by direct addition of water to the vinyl compound (II), we may return to a consideration of the precise nature of the reaction with alkali under the conditions of the kinetic experiments. Fig. 1 shows log k_2 for the alkaline fission of the sulphonium salts (I) at 0·005M-concentration plotted against Hammett's substituent constants, σ (Hammett, "Physical Organic Chemistry," McGraw-Hill,

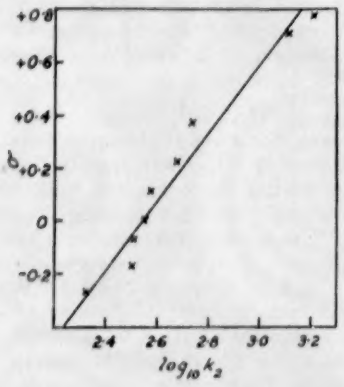


FIG. 1. *Correlation of rate of alkaline fission of* $Ar{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^-$ *with substitution in* Ar.

New York, 1940, p. 188). The line, drawn by the method of least squares, has the equation $\log k_2 = 2{\cdot}543 + 0{\cdot}768\,\sigma$; the correlation between structure and reaction velocity is good, the standard deviation, *s*, being 0·050 and the correlation coefficient, *r*, 0·987 (cf. Jaffé, *Chem. Rev.*, 1953, **53**, 191). No such correlation exists between σ and partial rate constants for elimination and substitution, calculated from the observed values of k_2 and the proportions of (II) and (III) found in the large-scale titration experiments (Table 4). This state of affairs is readily explicable if the system is such that the elimination reaction leading to (II) predominates in the early stages of the reaction, studied in the kinetic experiments, whereas the hydroxyethyl compound (III) is formed only at a late stage in the large-scale titration experiments. Such conditions obtain if the elimination reaction is reversible:

$$R{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2 + OH^- \rightleftharpoons R{\cdot}CO_2^- + CH_2{:}CH{\cdot}\overset{+}{S}Me_2 + H_2O$$

and is accompanied by irreversible direct hydrolysis:

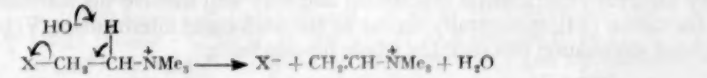
$$R{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2 + OH^- \longrightarrow R{\cdot}CO_2^- + HO{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2$$

providing that the rate of the forward elimination reaction is markedly greater than the rates of both the reverse reaction and the hydrolysis.

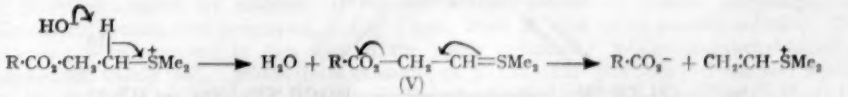
Under the conditions of our kinetic experiments, in which the concentrations of both water and hydroxyl ion were kept constant, the forward elimination reaction is of the first order whereas the reverse reaction is of the second order. In such a system, providing the rate constant for the reverse reaction is relatively small, the observed reaction will

closely approximate to first-order kinetics up to half-reaction. Thus, calculation shows that, if the rate constant for the reverse reaction is 10% of that for the forward reaction, the observed rate at half-reaction is 95% of that expected for the forward reaction alone; such a difference would hardly be detectable and would not appreciably upset the calculation of the first-order velocity constant; reference to Fig. 2 will show that some falling off from the first-order velocity was in fact observed. The reasonable correlation of k_2 with σ leads to the conclusion that the concomitant hydrolysis is in all cases slow compared with the elimination; accordingly we regard our k_2 values as reasonable measures of the rate of the forward elimination reaction.

This elimination reaction recalls the formally analogous elimination of hydrogen halides from 2-halogenoethyltrimethylammonium halides (Hofmann, *Jahresber.*, 1858, 339; Baeyer, *Annalen*, 1866, **140**, 311; Bode, *ibid.*, 1892, **267**, 268; Schmidt, *ibid.*, p. 300; *Apoth. Ztg.*, 1912, **27**, 682; Renshaw, *J. Amer. Chem. Soc.*, 1912, **34**, 1618; Renshaw and Ware, *ibid.*, 1925, **47**, 2993), the mechanism of which is clearly :



in which the attack on the α-hydrogen atom is facilitated by withdrawal of electrons under the influence of the ammonium pole. This reaction, however, is restricted to the favourable case in which X = halogen, only hydrolysis to choline being observed when X is an aroyloxy-group, and even then requiring more vigorous conditions than are required for the formation of (II) from (I). The observed enormous difference in alkali-lability between the sulphonium salts (I) and their ammonium analogues, clearly points to a more effective loosening of the α-hydrogen atom under the influence of the adjacent pole in the former case. On the basis of the ionisation potentials (nitrogen, 335 kcal./mole; sulphur, 239 kcal./mole), however, $-\overset{+}{S}R_2$ would be expected to be less powerful in attracting electrons than $-\overset{+}{N}R_3$ and this is borne out by its weaker *m*-orienting effect in aromatic substitution (Baker and Moffitt, *J.*, 1930, 1722; Pollard and Robinson, *ibid.*, p. 1765; Goss, Hanhart, and Ingold, *J.*, 1927, 250). For this reason we regard our elimination reaction as involving the sulphidimine-like intermediate (V), thus :



This pathway is, of course, not available in the ammonium series owing to the inability of nitrogen, unlike sulphur, to tolerate ten electrons in its outer shell; it is to this fundamental difference in the chemistry of sulphur and nitrogen that we ascribe the alkali-lability of the sulphonium salts (I) as compared with their nitrogen analogues.

The elimination reaction, as formulated above, calls for facilitation by electron-attracting substituents in R and this is in complete agreement with our experimental findings. Moreover, attack on (I) by hydroxyl ion occurs at a point distant from the benzene ring; this is borne out by the low value of +0·768 observed for the reaction constant, ρ. The reaction thus appears favourable for the evaluation of Hammett substituent constants, σ, for *ortho*-substituents. Calculation by Jaffé's method (*loc. cit.*) from the results in 0·005M-solution leads to the following σ values for the four *o*-substituents studied (the standard derivation is ±0·062) :

Substituent		*o*-NO_2	*o*-Cl	*o*-Me	*o*-MeO
σ		+0·703	+0·366	−0·054	−0·095
E_σ	Present work	+0·757	+0·420	0	−0·041
	Taft, *loc. cit.*	+0·95	+0·37	0	−0·24

Calculation from the less extensive series of results in 0·01M-solution leads to values not significantly different from the above. The sign and magnitude of the σ values for the

four *o*-substituents are in full accord with expectation. The Table also gives the E_σ values (Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 3120) obtained from the σ values by equating E_σ for the *o*-methyl group to zero; these may be compared with Taft's values (*loc. cit.*), obtained by a less direct method, which are given in the last line of the Table.

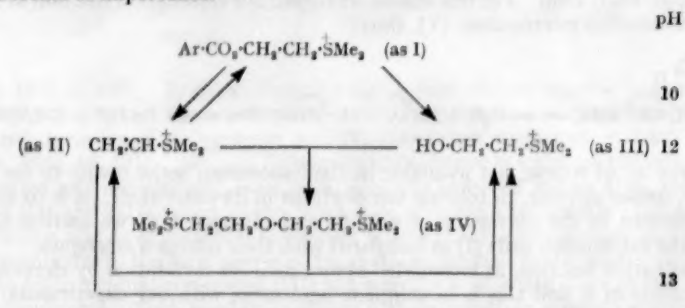
The unreactivity of sulphoxides compared with sulphones in this reaction is in conformity with the formulation of the latter alone as bearing a positive charge on the sulphur atom; such a positive charge is of importance for the necessary initial loosening of the attacked hydrogen atom.

The reverse elimination reaction clearly involves polarisation of the double bond in (II) and attack by a benzoate, or substituted benzoate, anion on the resulting, positively charged terminal carbon atom, followed by eventual recombination with a proton. This type of reaction, reminiscent of the addition reactions of the carbonyl group, is not known in the nitrogen series [the addition reactions of neurine, observed by Bode and Schmidt (*locc. cit.*) and referred to by Wenkert and Hansen (*Chem. and Ind.*, 1954, 1262) require very different experimental conditions] and may well involve the intermediate formation of the cation (VI), structurally similar to the unchanged intermediate (V) postulated in the forward elimination reaction, the whole process being:

$$\underset{\text{(as II)}}{CH_2{=}CH{-}\overset{+}{S}Me_2} \longrightarrow \underset{\text{(VI)}}{\overset{+}{C}H_2{-}CH{=}SMe_2} \xrightarrow{Ar{\cdot}CO_2^-} \underset{\text{(V)}}{Ar{\cdot}CO_2{\cdot}CH{\cdot}CH{=}SMe_2} \xrightarrow{H^+} \underset{\text{(as I)}}{Ar{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2}$$

Similar addition reactions, involving hydroxyl ion and the anion derived from (III), are clearly responsible for the formation of the hydroxylethyl compound (III) and the ether (IV) from the vinyl compound (II).

It is important to note that the reverse elimination, hydrolysis, and addition must all be involved in the formation of the ether (IV) from the vinyl compound (II) under conditions too weakly alkaline to allow the formation of the necessary hydroxyethyl compound (III) by direct addition of water to (II). The various reactions involved in the interconversion of the four sulphonium compounds are summarised in the annexed scheme, in which the figures at the side are the approximate minimum pH values at which the various reactions become of importance.



The hydrolysis by which (III) is formed directly from (II) seems likely to be of Ingold's $B_{AC}2$ type ("Structure and Mechanism in Organic Chemistry," Bell, Edinburgh, 1953, p. 754), involving attack by hydroxyl ion at the carbonyl carbon atom and, as such, facilitated by electron-attracting groups in R and subject to the *ortho*-effect; the experimental findings as to the effect of structure on the yield of the hydroxyethyl compound (III) in the large-scale titration experiments (Table 4) are in conformity with these requirements. The occurrence of this irreversible hydrolysis simultaneously with the reversible elimination leads to the conclusion that, at pH 10, any of the iodides (I) would eventually be converted entirely into the hydroxyethyl compound (III); although the period of contact with alkali at this pH was much longer in the large-scale titrations than in the kinetic experiments, it was never sufficient to allow complete conversion into (III) although 82% conversion was observed in the favourable case of the *p*-nitro-compound.

Experimental

2-Aroyloxyethyl Methyl Sulphides.—The aroyl chloride (1 mol.) was added in portions to 2-hydroxyethyl methyl sulphide (1 mol.) and pyridine (1·5—2·5 mols.), the temperature being kept below 30° by water cooling. After the addition was complete, the mixture was heated on the steam-bath for 2 hr. The semi-solid cooled reaction mixture was acidified with 2N-hydrochloric acid, and the product extracted with chloroform and distilled. The following were prepared in this way, in the yields indicated: 2-benzoyloxyethyl methyl sulphide (65%), b. p. 132°/2 mm.; methyl 2-*o*- (not purified), 2-*m*- (not purified), and 2-p-*nitrobenzoyloxyethyl sulphide* (83%), cream leaflets (from aqueous ethanol), m. p. 70° (Found: C, 50·2; H, 4·7. $C_{10}H_{11}O_4NS$ requires C, 49·8; H, 4·6%); 2-o- (80%), b. p. 110—111°/0·2 mm., n_D^{20} 1·5580 (Found: C, 52·1; H, 4·9. $C_{10}H_{11}O_2ClS$ requires C, 52·0; H, 4·8%), 2-m- (75%), b. p. 110°/0·15 mm., n_D^{20} 1·5550 (Found: C, 51·6; H, 5·0%), and 2-p-*chlorobenzoyloxyethyl methyl sulphide* (70%), b. p. 108°/0·1 mm., n_D^{20} 1·5594 (Found: C, 52·0; H, 4·9%); *methyl* 2-o- (87%), b. p. 100°/0·1 mm., n_D^{20} 1·5433 (Found: C, 62·7; H, 6·5. $C_{11}H_{14}O_2S$ requires C, 62·8; H, 6·7%), 2-m- (81%), b. p. 108°/0·2 mm., n_D^{20} 1·5419 (Found: C, 63·2; H, 7·1%), and 2-p-*toluoyloxyethyl sulphide* (79%), b. p. 108°/0·5 mm., n_D^{20} 1·5441 (Found: C, 63·3; H, 7·0%); 2-o- (79%), b. p. 132°/0·2 mm., n_D^{20} 1·5518 (Found: C, 58·3; H, 6·6. $C_{11}H_{14}O_3S$ requires C, 58·4; H, 6·2%), 2-m- (81%), b. p. 130°/0·2 mm., n_D^{20} 1·5485 (Found: C, 58·3; H, 6·3%), and 2-p-*anisoyloxyethyl methyl sulphide* (88%), b. p. 132°/0·2 mm., n_D^{20} 1·5560 (Found: C, 58·6; H, 6·6%).

2-p-*Aminobenzoyloxyethyl methyl sulphide.* Finely powdered methyl 2-*p*-nitrobenzoyloxyethyl sulphide (20 g.) and reduced iron (30 g.) in 80% aqueous ethanol (100 ml.) were boiled under reflux with stirring; addition of concentrated hydrochloric acid (0·5 ml.) resulted in an exothermic reaction which was moderated by water-cooling. After the initial reaction had subsided, heating was continued for 30 min. and the mixture filtered while hot. Concentration under reduced pressure brought about the separation of prismatic needles, m. p. 88—89° (15·9 g.); recrystallisation from ethanol afforded the *sulphide* (14·5 g., 83%) as needles, m. p. 89—90° (Found: C, 56·5; H, 6·2. $C_{10}H_{13}O_2NS$ requires C, 56·8; H, 6·2%). The N-*acetyl derivative*, obtained by heating the sulphide (1 g.) with acetic anhydride (3 ml.) at 100° for a few min., crystallised from aqueous ethanol in prismatic needles, m. p. 119—120° (Found: C, 56·7; H, 5·9. $C_{12}H_{15}O_3NS$ requires C, 56·9; H, 6·0%).

2-Aroyloxyethyldimethylsulphonium Halides.—(a) *Iodides.* The appropriate sulphide (1 mol.) was kept overnight, at room temperature, with methyl iodide (2 mols.), preferably in acetone solution. The iodide which separated was collected and recystallised, heating being kept to a minimum to avoid decomposition; a few iodides were converted into the corresponding picrates or picrylsulphonates by addition of aqueous sodium picrate or sodium picrylsulphonate (Golumbic, Fruton, and Bergmann, *J. Org. Chem.*, 1946, **11**, 518) to an aqueous solution. The following were prepared in this way in the yields indicated: 2-benzoyloxyethyldimethylsulphonium iodide (85%), plates (from ethanol), m. p. 132—133° (decomp.) [Crane and Rydon, *loc. cit.*, record m. p. 128—129° (decomp.)] (Found: C, 39·0; H, 4·5. Calc. for $C_{11}H_{15}O_2IS$: C, 39·1; H, 4·5%), characterised as the *picrylsulphonate*, needles (from methanol), m. p. 193—194° (decomp.) (Found: C, 40·9; H, 3·5. $C_{17}H_{17}O_{11}N_3S_2$ requires C, 40·6; H, 3·4%); *dimethyl*-2-o-*nitrobenzoyloxyethylsulphonium iodide* (37% overall), pale yellow flattened needles (from ethanol), m. p. 118° (decomp.) (Found: C, 34·8; H, 3·6. $C_{11}H_{14}O_4NIS$ requires C, 34·5; H, 3·7%); *dimethyl*-2-m-*nitrobenzoyloxyethylsulphonium iodide* (69% overall), pale yellow needles (from aqueous ethanol), m. p. 139·5° (decomp.) (Found: C, 35·0; H, 3·6%); *dimethyl*-2-p-*nitrobenzoyloxyethylsulphonium iodide* (79%), yellow needles (from aqueous ethanol), m. p. 138° (decomp.) (Found: C, 35·2; H, 3·8%), characterised as the *picrylsulphonate*, cream needles (from methanol), m. p. 181° (Found: C, 37·5; H, 2·9; N, 10·3. $C_{17}H_{16}O_{13}N_4S_2$ requires C, 37·2; H, 2·9; N, 10·2%); 2-o- (54%), stout needles (from ethanol), m. p. 101° (decomp.) (Found: C, 36·0; H, 3·8. $C_{11}H_{14}O_2SCII$ requires C, 35·5; H, 3·8%), 2-m- (55% overall), prismatic needles (from ethanol), m. p. 138° (decomp.) (Found: C, 36·0 H, 3·6%), and 2-p-*chlorobenzoyloxyethyldimethylsulphonium iodide* (51%), needles (from water), m. p. 153° (decomp.) (Found: C, 35·5; H, 3·7%); *dimethyl*-2-o-*toluoyloxyethylsulphonium iodide* (74%), white needles (from ethanol), m. p. 117—118° (decomp.) (Found: C, 41·2; H, 4·8. $C_{12}H_{17}O_2IS$ requires C, 40·9; H, 4·8%), characterised as the *picrate*, small yellow needles (from water), m. p. 170—171° (Found: C, 48·2; H, 4·7; N, 8·3. $C_{18}H_{19}O_9N_3S$ requires C, 48·1; H, 5·0; N, 8·4%), and *picrylsulphonate*, pale yellow needles (from methanol), m. p. 167° (Found: C, 41·7; H, 3·9; N, 8·4. $C_{14}H_{19}O_{11}N_3S_2$ requires C, 41·7; H, 3·7; N, 8·1%); *dimethyl*-2-m-*toluoyloxyethylsulphonium iodide* (64%), needles (from ethanol), m. p. 109—110°

(decomp.) (Found: C, 40·7; H, 5·0%); *dimethyl-2-p-toluoyloxyethylsulphonium iodide* (89%), rods (from methanol), m. p. 133·5° (decomp.) (Found: C, 40·8; H, 4·6%), characterised as the *picrylsulphonate*, flat needles (from aqueous ethanol), m. p. 151° (Found: C, 41·8; H, 3·9; N, 8·3. $C_{18}H_{19}O_{11}N_3S_2$ requires C, 41·7; H, 3·7; N, 8·1%); *2-o-anisoyloxyethyldimethylsulphonium iodide* (65%), needles (from ethanol), m. p. 110—111° (decomp.) (Found: C, 39·3; H, 4·6. $C_{12}H_{17}O_3IS$ requires C, 39·1; H, 4·7%), characterised as the *picrylsulphonate*, cream-coloured cubes (from methanol), m. p. 184—185° (Found: C, 40·3; H, 3·6; N, 7·9. $C_{18}H_{19}O_{12}N_3S_2$ requires C, 40·5; H, 3·6; N, 7·9%); 2-m- (74%), needles (from ethanol), m. p. 129° (decomp.) (Found: C, 39·4; H, 4·6%), and 2-p-*anisoyloxyethyldimethylsulphonium iodide* (66%), leaflets (from ethanol), m. p. 126—127·5° (decomp.) (Found: C, 38·8; H, 4·5%).

The solubilities of the iodides in water at 25°, determined by estimating iodide ion in saturated solutions prepared (*a*) by stirring the finely powdered salt with water at 25° and (*b*) by allowing hot saturated solutions to cool to 25° with stirring, are given in Table 2. The great solubility of the *o*-methoxy-compound is surprising.

TABLE 2. *Solubility in water at 25° of 2-aroyloxyethyldimethylsulphonium iodides,* $R{\cdot}C_6H_4{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^-$.

R	H	*o*-NO_2	*m*-NO_2	*p*-NO_2	*o*-Cl	*m*-Cl	*p*-Cl
Solubility (moles/l.) ...	0·194	0·062	0·031	0·023	0·102	0·034	0·011
R	*o*-Me	*m*-Me	*p*-Me	*o*-MeO	*m*-MeO	*p*-MeO	
Solubility (moles/l.) ...	0·076	0·122	0·043	0·537	0·055	0·063	

(b) *Chlorides.* The appropriate sulphonium iodide was stirred or shaken with an excess of freshly precipitated silver chloride. After filtration, the solution was evaporated to dryness under reduced pressure and the residue of sulphonium chloride recrystallised. The following were prepared in this way in the yield indicated: *2-benzoyloxyethyldimethylsulphonium chloride* (69%), deliquescent prisms (from absolute ethanol and anhydrous ether), m. p. 152° (decomp.) (Found: C, 53·6; H, 6·2. $C_{11}H_{15}O_2ClS$ requires C, 53·8; H, 6·1%); *dimethyl-2-m-nitrobenzoyloxyethylsulphonium chloride* (81%), needles (from absolute ethanol), m. p. 136—137° (decomp.) (Found: C, 45·2; H, 4·5. $C_{11}H_{14}O_4NClS$ requires C, 45·3; H, 4·8%); *dimethyl-2-p-nitrobenzoyloxyethylsulphonium chloride monohydrate* (87%), needles (from ethanol), m. p. 109° (decomp.) (Found: C, 42·7; H, 5·0. $C_{11}H_{14}O_4NClS,H_2O$ requires C, 42·7; H, 5·2%); *dimethyl-2-p-toluoyloxyethylsulphonium chloride* (60%), needles (from ethanol–ether), m. p. 148° (decomp.) (Found: C, 55·0; H, 6·2. $C_{12}H_{17}O_2ClS$ requires C, 55·3; H, 6·5%); *2-p-chlorobenzoyloxyethyldimethylsulphonium chloride* (68%), prismatic needles (from ethanol), m. p. 166° (decomp.) (Found: C, 46·9; H, 5·0. $C_{11}H_{14}O_2Cl_2S$ requires C, 46·6; H, 4·9%).

2-Aroyloxyethyl Methyl Sulphones and Sulphoxides.—2-Benzoyloxyethyl methyl sulphide (10 g.), in acetone (20 ml.), was treated at room temperature with aqueous hydrogen peroxide (5·8 ml. of 30%) in acetone (20 ml.). After being kept overnight, the solution was evaporated under reduced pressure, leaving an oil which crystallised in a vacuum-desiccator. Recrystallisation from ether–light petroleum (b. p. 40—60°) gave *2-benzoyloxyethyl methyl sulphoxide* (8·1 g., 75%) as prisms, m. p. 62—65°; a second crop (2·0 g., 18%), m. p. 59—62°, was obtained from the mother-liquor. The analytical sample, obtained by further recrystallisation, had m. p. 65—66° (Found: C, 57·0; H, 5·7. $C_{10}H_{12}O_3S$ requires C, 56·6; H, 5·6%).

This sulphoxide (6 g.), in acetone (20 ml.), was treated at room temperature with a saturated solution of potassium permanganate in acetone until no further oxidation occurred. Filtration, evaporation of the filtrate, and recrystallisation from aqueous ethanol afforded *2-benzoyloxyethyl methyl sulphone* (6 g., 93%) as prismatic needles, m. p. 62·5—63·5° (Found: C, 52·6; H, 5·3. $C_{10}H_{12}O_4S$ requires C, 52·6; H, 5·1%). Alternatively, 2-benzoyloxyethyl methyl sulphide (11·3 g.), in acetic acid (30 ml.), was heated on the steam-bath while aqueous hydrogen peroxide (25 ml. of 30%) was added in portions. After the initial vigorous reaction had abated, the mixture was heated for a further 1½ hr. and evaporated under reduced pressure. Crystallisation from aqueous ethanol afforded the sulphone (9·8 g., 74%), m. p. 62·5—63·5°.

Methyl *2-p*-nitrobenzoyloxyethyl sulphide (15 g.), in acetic acid (45 ml.), was gently refluxed while aqueous hydrogen peroxide (32 ml. of 30%) was added in portions. The mixture was then refluxed for a further hour and then evaporated to dryness under reduced pressure. Recrystallisation from ethanol–"Ethyl cellosolve" afforded *methyl 2-p-nitrobenzoyloxyethyl sulphone* (12·5 g., 74%) as pale yellow needles, m. p. 137—138° (Found: C, 44·4; H, 4·2. $C_{10}H_{11}O_6NS$ requires C, 43·9; H, 4·1%).

2-Benzoyloxyethyl Ethyl Sulphide and its Derivatives.—Ethyl 2-hydroxyethyl sulphide

(20 g.; Demuth and Meyer, *Annalen*, 1887, **240**, 310) in pyridine (25 ml.) was slowly treated with benzoyl chloride (26·5 g.), and the mixture heated on the steam-bath for 2 hr. The *sulphide* (33·8 g., 79%), isolated in the usual manner, had b. p. 86—88°/0·03 mm. (Found: C, 63·1; H, 6·7. $C_{11}H_{14}O_2S$ requires C, 62·9; H, 6·7%); this compound was prepared by Davis and Ross (*J.*, 1950, 3061) who, however, record neither b. p. nor analytical data.

The sulphide (5·0 g.) was kept overnight with methyl iodide (8 g.). Recrystallisation of the deposited solid from ethanol yielded *2-benzoyloxyethylethylmethylsulphonium iodide* (6·6 g., 85%), as needles, m. p. 106—107° (decomp.), raised to 110—111° (decomp.) by further recrystallisation (Found: C, 41·3; H, 4·8. $C_{12}H_{17}O_2IS$ requires C, 40·9; H, 4·9%).

The sulphide (1 g.), in acetic acid (8 ml.), was treated with aqueous hydrogen peroxide (6 ml. of 30%) and the mixture boiled under reflux for 1 hr. Evaporation and recrystallisation from ethanol–light petroleum (b. p. 60—80°) yielded *2-benzoyloxyethyl ethyl sulphone* (0·75 g., 65%) as flat needles, m. p. 38° (Found: C, 54·5; H, 5·8. $C_{11}H_{14}O_4S$ requires C, 54·5; H, 5·8%).

2-Aroyloxyethyl Aryl Sulphides and Sulphones.—2-Hydroxylethyl phenyl sulphide (23·9 g.; Kirner and Richter, *J. Amer. Chem. Soc.*, 1929, **51**, 3413), in pyridine (25 ml.), was slowly treated with benzoyl chloride (22·2 g.), and the mixture heated on the steam-bath for 30 min. Isolation in the usual manner afforded *2-benzoyloxyethyl phenyl sulphide* (30·5 g., 70%), b. p. 134°/0·05 mm. (Found: C, 70·2; H, 6·0. $C_{15}H_{14}O_2S$ requires C, 69·8; H, 5·5%). This sulphide (5·5 g.), in acetic acid (15 ml.), was treated with aqueous hydrogen peroxide (12·5 ml. of 30%), and the mixture boiled under reflux for 30 min. Addition of water and recrystallisation of the precipitate from ethanol afforded *2-benzoyloxyethyl phenyl sulphone* (5·5 g., 89%) as long needles, m. p. 123° (Found: C, 62·3; H, 4·9. $C_{15}H_{14}O_4S$ requires C, 62·1; H, 4·9%).

2-Hydroxyethyl phenyl sulphide (2·4 g.), in pyridine (3·5 ml.), was slowly treated with *p*-nitrobenzoyl chloride (2·9 g.), and the mixture heated on the steam-bath for 1 hr. Working up in the usual manner, followed by recrystallisation from aqueous ethanol, afforded *2-p-nitrobenzoyloxyethyl phenyl sulphide* (3·0 g., 64%) as pale yellow prisms, m. p. 52—54° (Found: C, 59·3; H, 4·4. $C_{15}H_{13}O_4NS$ requires C, 59·4; H, 4·4%).

2-Hydroxyethyl *o*-nitrophenyl sulphide (5·0 g.; Bennett and Berry, *J.*, 1927, 1668) was benzoylated as usual with benzoyl chloride (3·6 g.) in pyridine (11 ml.); *2-benzoyloxyethyl o-nitrophenyl sulphide* (7·4 g., 97%) cystallised from ethanol in lemon-yellow prismatic needles, m. p. 111—112° (Found: C, 59·3; H, 4·4. $C_{15}H_{13}O_4NS$ requires C, 59·4; H, 4·3%); oxidation of this sulphide (0·5 g.) with 30% aqueous hydrogen peroxide (3 ml.) in acetic acid (5 ml.) yielded *2-benzoyloxyethyl o-nitrophenyl sulphone* (0·48 g., 87%), pale yellow needles (from aqueous ethanol), m. p. 99—100° (Found: C, 54·0; H, 4·0. $C_{15}H_{13}O_6NS$ requires C, 53·7; H, 3·9%). *2-Benzoyloxyethyl* p-*nitrophenyl sulphide*, prepared as for the *o*-isomer, crystallised from ethanol in pale yellow prismatic needles, m. p. 60—61° (Found: C, 59·6; H, 4·5%).

3-Aroyloxypropyl Methyl Sulphides and Derivatives.—Benzoylation of 3-hydroxypropyl methyl sulphide (21·2 g.; Kirner, *J. Amer. Chem. Soc.*, 1928, **50**, 2452) with benzoyl chloride (29 g.) in pyridine (25 ml.) for 6 hr. at 100° afforded *3-benzoyloxypropyl methyl sulphide* (40·7 g., 94%), b. p. 116—118°/0·04 mm. (Found: C, 62·5; H, 6·9. $C_{11}H_{14}O_2S$ requires C, 62·8; H, 6·7%); this sulphide (40 g.), kept overnight with methyl iodide (50 g.), afforded *3-benzoyloxypropyldimethylsulphonium iodide* (53·5 g., 78%), prisms (from ethanol), m. p. 100° (decomp.) (Found: C, 41·4; H, 4·8. $C_{12}H_{17}O_2IS$ requires C, 40·9; H, 4·9%).

Methyl 3-*p*-nitrobenzoyloxypropyl sulphide, prepared from 3-hydroxypropyl methyl sulphide (23 g.) in pyridine (30 ml.) and *p*-nitrobenzoyl chloride (44·5 g.) in benzene (40 ml.) at 100° for 6 hr., could not be induced to crystallise and was kept overnight with methyl iodide (50 g.); *dimethyl-3-p-nitrobenzoyloxypropylsulphonium iodide* (53·5 g., 56%), so obtained, crystallised from ethanol in golden-yellow needles, m. p. 116° (decomp.) (Found: C, 36·4; H, 3·8. $C_{12}H_{16}O_4NIS$ requires C, 36·3; H, 4·1%).

4-Benzoyloxybutyl Methyl Sulphide.—4-Chlorobutyl benzoate (30 g.; Synerholm, *Org. Synth.*, 1949, **29**, 30) was slowly added to a solution of sodium methyl sulphide (0·15 mol.) in methanol and the mixture refluxed for 1 hr. Evaporation, addition of water, extraction with ether, and distillation of the dried extract afforded the *sulphide* (12·5 g., 40%), b. p. 100—101°/0·07 mm. (Found: C, 64·4; H, 7·0. $C_{12}H_{16}O_2S$ requires C, 64·2; H, 7·2%); the derived *4-benzoyloxybutyldimethylsulphonium iodide* crystallised from ethanol in needles, m. p. 118—119° (decomp.) (Found: C, 42·8; H, 5·1; I, 34·9. $C_{13}H_{19}O_2IS$ requires C, 42·6; H, 5·2; I, 34·6%).

Neither *4-chlorobutyl* p-*nitrobenzoate*, prepared as usual in 54% yield from tetramethylene chlorohydrin, needles (from ethanol containing a little acetone), m. p. 39° (Found: N, 5·0; Cl, 13·9. $C_{11}H_{12}O_4NCl$ requires N, 5·4; Cl, 13·8%), nor 5-chloropentyl benzoate (Synerholm,

J. Amer. Chem. Soc., **1947**, **69**, 2581) could be induced to react with sodium methyl sulphide to form the corresponding sulphides.

Choline Derivatives.—Potassium benzoate (58 g.; dried at 130°/20 mm.) was added to a solution of 2-dimethylaminoethyl chloride (from the hydrochloride, 51 g.) in toluene (200 ml.), and the mixture refluxed for 18 hr. The hot mixture was filtered, the solid was washed with hot toluene, and the combined filtrates were distilled, giving 2-dimethylaminoethyl benzoate (40 g.), b. p. 99—105°/1 mm. This was dissolved in acetone (300 ml.), then treated with methyl iodide (37 g.), and the mixture kept overnight. The precipitated leaflets were collected and recrystallised from methanol; 2-benzoyloxyethyltrimethylammonium iodide (64 g., 93%) so obtained had m. p. 246—247° (decomp.) [lit., m. p. 247° (decomp.)] (Found: C, 42·9; H, 5·4. Calc. for $C_{12}H_{18}O_2NI$: C, 43·0; H, 5·4%).

2-Dimethylaminoethyl *p*-nitrobenzoate (40 g.; Einhorn, Fiedler, Ladisch, and Uhlfelder, *Annalen*, **1910**, **371**, 142) and methyl iodide (40 g.) were kept in acetone (300 ml.) overnight. The precipitated *trimethyl-2-p-nitrobenzoyloxyethylammonium iodide* (61 g., 96%) crystallised from ethanol in yellow needles, m. p. 255—256° (decomp.) (Found: C, 37·9; H, 4·4; N, 7·4. $C_{12}H_{17}O_4N_2I$ requires C, 37·9; H, 4·5; N, 7·4%).

Kinetic experiments.

The action of alkali on the sulphonium salts was followed by continuous titration with sodium hydroxide (0·1 or 0·2N) in the apparatus described by Powell and Trendall (*Chem. and Ind.*, **1943**, **62**, 368), the reaction vessel being immersed in a thermostat at 25° ± 0·02°. Successive volumes (0·02 ml.) of standard alkali were added whenever the pH reached the desired

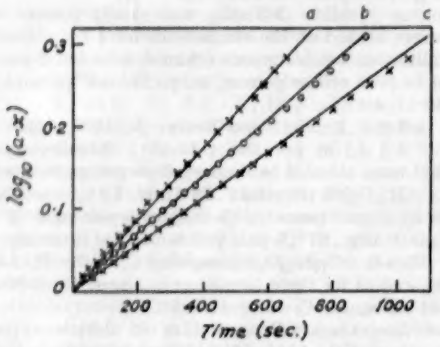


FIG. 2. *Alkaline fission of* p-$NO_2{\cdot}C_6H_4{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^-$ *in 0·01M-solution at 25°.*
a, pH 9·66; *b*, pH 9·55; *c*, pH 9·45.

minimum value, as determined by matching the colour of the internal indicator with that of a solution of the same indicator in a suitable borate buffer contained in a vessel placed alongside the reaction vessel; the time at which each addition of alkali was made was noted.

After numerous trials the following indicator mixtures (Kolthoff and Rosenbloom, "Acid–Base Indicators," MacMillan, London, **1937**, p. 173) were found suitable:

	Acid colour	Alkaline colour
A. Phenolphthalein and α-naphtholphthalein; 2 : 1; both 0·1% in 50% aqueous ethanol	Green	Violet-red
B. Alizarin-yellow G and xylene-cyanol FF; 1 : 1·5; both 0·1% in ethanol	Green	Red
C. Thymolphthalein and alizarin-yellow G; 2 : 1; both 0·1% in ethanol	Grey	Rose

The mean pH quoted is the mean of the pH at which each fresh addition of alkali was made and the calculated pH of the solution immediately after each addition of alkali.

At least three runs were carried out at each pH for each concentration of each sulphonium salt. The agreement between runs was good. First-order velocity constants, k_1, were calculated in the usual way from plots of $\log_{10}(a - x)$ against time, the times being the means of those determined in the individual runs; the log plots were satisfactorily linear, the deviation from linearity being such as to make the uncertainty of k_1 only ±3%; Fig. 2 shows the log plots for dimethyl-2-*p*-nitrobenzoyloxyethylsulphonium iodide in 0·01M-solution at three pH values. $\text{Log}_{10} k_2$ was obtained by adding the mean pOH to $\log_{10} k_1$. The results are summarised in Table 3; full experimental details are given by Mamalis (Ph.D. Thesis, London, **1953**).

TABLE 3. *Rate constants for alkaline fission of aroyloxyalkylsulphonium halides at 25°.*

(1) Concn. (M)	(2) Indicator	(3) pH Min.	(4) pH Mean	(5) 10^4k_1 (min.$^{-1}$)	(6) log k_2	(7) Mean log k_2	(8) Mean k_2 (l. mole^{-1} min.$^{-1}$)
2-Benzoyloxyethyldimethylsulphonium iodide							
0·005	B	9·60	9·87	268	2·558	2·552	356·5
		10·00	10·24	611	2·546		
0·0075	B	9·60	9·99	336	2·536	2·508	322·1
		9·80	10·11	394	2·484		
		10·00	10·24	564	2·511		
0·01	A	9·00	9·66	119	2·415	2·454	284·4
		9·30	9·82	193	2·465		
	C	9·60	9·99	291	2·474		
		9·60	10·12	376	2·455		
	B	10·00	10·35	645	2·459		
2-Benzoyloxyethyldimethylsulphonium chloride							
0·005	A	9·30	9·69	148	2·480	2·507	321·4
	B	9·60	9·87	251	2·530		
		10·00	10·15	458	2·511		
0·01	A	9·00	9·66	130	2·454	2·469	294·4
		9·30	9·82	197	2·475		
	B	9·60	9·99	294·5	2·479		
0·005	A	8·80	9·41	323	3·100	3·094	1242
		9·00	9·52	401	3·083		
		9·30	9·69	617	3·100		
0·005 + 0·005M-KI	A	8·60	9·31	230	3·052	3·060	1148
		8·80	9·41	292	3·055		
		9·00	9·52	392	3·073		
0·01	A	8·60	9·45	334	3·074	3·066	1164
		8·80	9·55	433	3·086		
		9·00	9·66	532	3·066		
		9·30	9·82	717	3·036		
Dimethyl-2-*m*-nitrobenzoyloxyethylsulphonium iodide							
0·005	A	8·80	9·41	320	3·095	3·109	1285
		9·00	9·52	419	3·102		
		9·30	9·69	662	3·131		
0·01	A	8·60	9·45	308	3·039	3·036	1086
		8·80	9·55	392	3·043		
		9·00	9·66	488	3·028		
		9·30	9·82	714	3·034		
Dimethyl-2-*p*-nitrobenzoyloxyethylsulphonium iodide							
0·002	A	8·60	9·23	366	3·333	3·314	2061
		8·80	9·37	463	3·296		
		9·00	9·475	616	3·315		
0·005	A	8·60	9·31	334	3·214	3·207	1611
		8·80	9·41	407	3·200		
		9·00	9·52	534	3·207		
0·0075	A	8·60	9·45	481	3·232	3·206	1607
		8·80	9·55	573	3·208		
		9·00	9·65	671	3·177		
0·005 + 0·005M-KI	A	8·60	9·31	312	3·184	3·183	1524
		8·80	9·41	383	3·173		
		9·00	9·52	484	3·175		
		9·30	9·69	780	3·202		
0·01	A	8·60	9·45	392	3·143	3·133	1358
		8·80	9·55	477	3·127		
		9·00	9·66	600	3·128		
2-*o*-Chlorobenzoyloxyethyldimethylsulphonium iodide							
0·005	A	9·00	9·52	221	2·824	2·828	673·0
		9·30	9·69	331	2·830		
	B	9·60	9·87	500	2·829		

TABLE 3. (*Continued.*)

(1) Concn. (M)	(2) Indicator	(3) pH Min.	(4) pH Mean	(5) 10^4k_1 (min.$^{-1}$)	(6) log k_2	(7) Mean log k_2	(8) Mean k_2 (l. mole^{-1} min.$^{-1}$)
2-*o*-Chlorobenzoyloxyethyldimethylsulphonium iodide (*cont.*)							
0·01	A	9·00	9·66	286	2·796	2·775	595·7
	A	9·30	9·82	413	2·796		
	B	9·60	9·99	564	2·761		
	B	9·80	10·11	720	2·747		
2-*m*-Chlorobenzoyloxyethyldimethylsulphonium iodide							
0·005	A	9·00	9·52	175	2·733	2·735	543·3
	A	9·30	9·69	276	2·751		
	B	9·60	9·87	392	2·722		
0·01	A	8·80	9·55	168	2·675	2·692	492·0
	A	9·00	9·66	212	2·666		
	A	9·30	9·82	357	2·733		
2-*p*-Chlorobenzoyloxyethyldimethylsulphonium iodide							
0·002	A	9·00	9·475	143	2·679	2·710	512·9
	A	9·30	9·65	242	2·734		
	B	9·60	9·84	360	2·717		
0·005	A	9·00	9·52	144	2·638	2·678	476·4
	A	9·30	9·69	230	2·672		
	A	9·30	9·82	332	2·701		
	B	9·60	9·99	474	2·686		
	B	10·00	10·24	859	2·694		
Dimethyl-2-*o*-toluoyloxyethylsulphonium iodide							
0·005	B	9·60	9·87	251	2·530	2·497	314·1
	B	9·80	10·00	326	2·513		
	B	10·00	10·15	396	2·448		
0·01	B	9·60	9·99	246	2·401	2·387	243·8
	B	9·80	10·11	314	2·387		
	B	10·00	10·24	411	2·374		
Dimethyl-2-*m*-toluoyloxyethylsulphonium iodide							
0·005	B	9·60	9·87	242	2·514	2·508	322·1
	B	9·80	10·00	331	2·520		
	B	10·00	10·15	435	2·489		
0·01	A	9·30	9·82	182	2·440	2·435	272·3
	B	9·60	9·99	258	2·422		
	B	9·80	10·11	357	2·443		
Dimethyl-2-*p*-toluoyloxyethylsulphonium iodide							
0·005	B	9·60	9·99	322	2·518	2·504	319·2
	B	9·80	10·11	401	2·493		
	B	10·00	10·24	550	2·500		
0·01	A	9·30	9·82	158	2·379	2·389	244·9
	C	9·60	9·99	246	2·401		
	B	9·60	10·12	333	2·402		
	B	10·00	10·35	534	2·378		
	B	10·40	10·60	964	2·384		
2-*o*-Anisoyloxyethyldimethylsulphonium iodide							
0·005	A	9·30	9·69	149	2·483	2·464	291·1
	B	9·60	9·87	220	2·472		
	B	9·80	10·00	273	2·436		
0·01	A	9·00	9·66	127	2·442	2·426	266·7
	A	9·30	9·82	180	2·435		
	B	9·60	9·99	246	2·401		
2-*m*-Anisoyloxyethyldimethylsulphonium iodide							
0·005	A	9·30	9·60	181	2·568	2·571	372·4
	B	9·60	9·87	246	2·521		
	B	10·00	10·15	376	2·625		
0·01	A	9·30	9·82	199	2·379	2·417	261·2
	B	9·60	9·99	256	2·418		
	B	10·00	10·24	495	2·455		

TABLE 3. (*Continued.*)

(1) Concn. (M)	(2) Indicator	(3) pH Min.	(4) pH Mean	(5) 10^4k_1 (min.$^{-1}$)	(6) log k_2	(7) Mean log k_2	(8) Mean k_2 (l. mole^{-1} min.$^{-1}$)
2-*p*-Anisoyloxyethyldimethylsulphonium iodide							
0·005	B	9·60	9·99	221	2·354	2·328	212·8
		9·80	10·11	259	2·303		
		10·00	10·24	360	2·316		
0·01	B	9·80	10·23	300	2·247	2·251	178·2
		10·00	10·35	378	2·227		
		10·40	10·60	756	2·278		
Dimethyl-3-*p*-nitrobenzoyloxypropylsulphonium iodide							
0·005	A	9·00	9·52	117	2·548	2·565	367·3
		9·30	9·69	181	2·567		
	B	9·60	9·87	282	2·580		
0·01	A	9·00	9·66	147	2·507	2·516	328·1
		9·30	9·82	216	2·514		
	B	9·60	9·99	328	2·526		

Isolation of fission products.

Synthesis of Reference Compounds.—Dimethylvinylsulphonium picrysulphonate. A mixture of 2-chloroethyl methyl sulphide (11·0 g.; Kirner and Windus, *Org. Synth.*, 1943, Coll. Vol. 2, 136) and methyl iodide (16 g.) was kept at room temperature overnight; the precipitate was collected, washed with ether, and recrystallised from ethanol–ether, affording *2-chloroethyldimethylsulphonium iodide*, (9·5 g., 38%), white needles, m. p. 90—91° (Found: C, 18·5; H, 3·8. $C_4H_{10}SClI$ requires C, 19·0; H, 4·0%), characterised as its *picrylsulphonate*, needles (from methanol), m. p. 218° (Found: C, 28·5; H, 2·5. $C_{10}H_{13}O_9N_3S_2Cl$ requires C, 28·7; H, 2·9%). The above methiodide (3·78 g.), in water (280 ml.) containing sodium hydrogen carbonate (6·3 g.), was treated with sodium hydroxide (0·6 g.), and the mixture kept at 20° for 2 days. After the pH had been adjusted to 5 with 2N-hydrochloric acid, sodium picrylsulphonate (4 g.) was added and the solution concentrated under reduced pressure to 50 ml. The solid which separated on cooling [4·2 g., 90%; m. p. 199—200° (decomp.)] was recrystallised from methanol; *dimethylvinylsulphonium picrylsulphonate* forms flat cream-coloured needles, m. p. 199—200° (decomp.) (Found: C, 31·7; H, 2·9; N, 11·4; S, 16·9. $C_{10}H_{11}O_9N_3S_2$ requires C, 31·5; H, 2·9; N, 11·0; S, 16·8%).

2-Hydroxyethyldimethylsulphonium picrylsulphonate. 2-Hydroxyethyl methyl sulphide (9·2 g.), in acetone (20 ml.), was treated, with cooling, with methyl iodide (16 g.), and the mixture kept overnight. The precipitate [12 g., 51%; m. p. 55—57° (decomp.)] was collected, washed with acetone, and recrystallised from ethanol, yielding *2-hydroxyethyldimethylsulphonium iodide*, as large deliquescent plates, m. p. 56—57° (decomp.) (Found: I, 53·7. $C_4H_{11}OIS$ requires I, 54·3%). Challenger and Simpson (*J.*, 1948, 1591) record m. p. 56—57° (decomp.), but give no analysis. The *picrylsulphonate* crystallised from methanol in needles, m. p. 169—170° (Found: C, 30·1; H, 3·2. $C_{10}H_{13}O_{10}N_3S_2$ requires C, 30·1; H, 3·3%).

Dithian monomethopicrylsulphonate. 1 : 4-Dithian (1·0 g.; Fuson, Lipscomb, McKusick, and Reed, *J. Org. Chem.*, 1946, 11, 516) and methyl iodide (1 ml.) were refluxed in ethanol (10 ml.) for 12 hr. The precipitated methiodide was collected and converted in the usual manner into the *picrylsulphonate*, long yellow needles (from water), m. p. 240—242° (decomp.) (Found: C, 31·1; H, 3·1; N, 10·3. $C_{11}H_{13}O_9N_3S_3$ requires C, 30·9; H, 3·1; N, 9·8%).

Dimethyl-2-methylthioethylsulphonium picrylsulphonate. The iodide (Crane and Rydon, *loc. cit.*) was treated with sodium picrylsulphonate in the usual manner; two recrystallisations from water yielded the *picrylsulphonate* as needles (cubes by slow cooling), m. p. 160° (resolidifying and decomp. above 200°) (Found: C, 30·9; H, 3·5; N, 10·0. $C_{11}H_{15}O_9N_3S_3$ requires C, 30·8; H, 3·5; N, 9·8%).

Derivatives of bis-2-methylthioethyl ether. Bis-2-mercaptoethyl ether (5 g.) (Hull, Weinland, Olsen, and France, *Ind. Eng. Chem.*, 1948, 40, 513) was dissolved in aqueous sodium hydroxide (3 g. in 20 ml. of water) and treated with methyl sulphate (7 ml.) in one portion. After 2 hr. the mixture was extracted with ether; distillation of the dried extract afforded *bis-2-methylthioethyl ether*, b. p. 110°/11 mm. (Found: C, 43·6; H, 8·2; S, 37·6. $C_6H_{14}OS_2$ requires C, 43·4; H, 8·5; S, 38·6%).

This ether (1 g.) was kept overnight with methyl iodide (2 ml.). Trituration of the product

with dry ether, followed by crystallisation from ethanol containing a little water, afforded the *bismethiodide*, prismatic needles, m. p. 142—143° (decomp.) (Found: C, 21·6; H, 4·2; I, 56·0. $C_8H_{20}OS_2I_2$ requires C, 21·3; H, 4·3; I, 56·4%); stirring an aqueous solution with freshly precipitated silver chloride, followed by filtration, evaporation, repeated evaporation with dry ethanol, and recrystallisation from anhydrous ethanol–ether, gave the *bismethochloride*, prisms, m. p. 196—197° (decomp.) (Found: Cl, 25·4. $C_8H_{20}OS_2Cl_2$ requires Cl, 25·1%). The *bismethopicrylsulphonate*, prepared from the iodide in the usual manner, crystallised from water in cream-coloured leaflets, m. p. 215—216° (Found: C, 30·8; H, 3·1; N, 10·6. $C_{20}H_{24}O_{19}N_6S_4$ requires C, 30·8; H, 3·1; N, 10·8%).

The ether (1 g.), dissolved in warm acetic acid (10 ml.), was treated in portions with 30% aqueous hydrogen peroxide (3 ml.). After the initial vigorous reaction had abated, the mixture was heated on the steam-bath for an hour and then evaporated under reduced pressure. Two crystallisations of the residue from chloroform–light petroleum (b. p. 40—60°) yielded *bis-2-methylsulphonylethyl ether* as prismatic needles, m. p. 78° (Found: C, 31·4; H, 6·3. $C_6H_{14}O_6S_2$ requires C, 31·3; H, 6·1%).

Allyldimethylsulphonium picrylsulphonate. Allyl iodide (2·1 g.) and dimethyl sulphide (0·8 g.) were kept overnight in ether (10 ml.). The oily methiodide remaining after decantation of the ether was dissolved in water (20 ml.) and treated with sodium picrylsulphonate (1·5 g.) in a little water. Two recrystallisations of the precipitate from methanol afforded the *picrylsulphonate* as needles, m. p. 175—176° (Found: C, 33·8; H, 3·4; N, 10·7. $C_{11}H_{13}O_9N_3S_2$ requires C, 33·4; H, 3·3; N, 10·6%).

3-Hydroxypropyldimethylsulphonium picrylsulphonate. 3-Hydroxypropyl methyl sulphide (1 g.) and methyl iodide (2 ml.) were mixed and kept at room temperature overnight. The oily product was washed with ether, dissolved in water (15 ml.), and treated with sodium picrylsulphonate (1·5 g.) in a little water. Two crystallisations from methanol yielded the *picrylsulphonate* as pale yellow needles, m. p. 155° (Found: C, 32·2; H, 3·8; N, 10·6. $C_{11}H_{15}O_{10}N_3S_2$ requires C, 32·0; H, 3·6; N, 10·2%).

2-Hydroxyethyltrimethylammonium picrylsulphonate, prepared in the usual way from choline chloride and sodium picrylsulphonate, crystallised from methanol in needles, m. p. 245° (decomp.) (Found: C, 33·4; H, 4·1; N, 14·2. $C_{11}H_{16}O_{10}N_4S$ requires C, 33·3; H, 4·1; N, 14·1%).

Reactions under Titration Conditions.—(a) *2-Aroyloxyethyldimethylsulphonium iodides.* A solution of the sulphonium iodide (0·01 mole) in water (1 l.) containing a few drops of indicator was stirred mechanically at 25° while N-sodium hydroxide was added dropwise; fresh alkali was added when the pH reached 9·3 (indicator A) or 10·0 (indicator B). pH control was necessarily less precise in these experiments than in the kinetic runs; the mean pH was about 9·8 with indicator A and 10·2 with B. When 1 equiv. (10 ml.) of alkali had been added, the solution was acidified by addition of N-hydrochloric acid (10 ml.), and the benzoic acid (theoretical yield) removed by extraction with ether (3 × 100 ml.). Sodium picrylsulphonate (3·15 g., 0·01 mole) was added to the residual aqueous solution which was then concentrated under reduced pressure at below 35°. Crops of crystals were collected at various stages during the concentration and their compositions determined from a mixed m. p. curve constructed by using mixtures of authentic dimethylvinyl- and dimethyl-2-hydroxyethyl-sulphonium picrylsulphonates; mixtures containing 60% or more of the hydroxy-compound were recrystallised before having recourse to the m. p. curve; the m. p. bath was preheated to 165° for mixtures containing less than 50% of the hydroxy-compound and to 160° for mixtures containing more than 50%. Correction for solubility was made on the basis of separations of known mixtures of the two picrylsulphonates in the presence of the equivalent of sodium iodide; the correction factor for the vinyl compound was 1·11 and for the hydroxy-compound, 1·33.

In a typical experiment, 2-benzoyloxyethyldimethylsulphonium iodide (3·38 g.) in water (1 ml.), titrated with N-sodium hydroxide (10 ml.) and indicator B, gave the following crops: (*a*) At 200 ml., pale yellow needles, m. p. 198—199°, 0·95 g., 99% vinyl; (*b*) at 100 ml., flat yellow needles, m. p. 198—199°, 0·90 g., 99% vinyl; (*c*) at 70 ml., small yellow needles, m. p. 197—198°, 0·40 g., 97% vinyl; (*d*) at 30 ml., felted pale yellow needles, m. p. 166—169° (not depressed by authentic 2-hydroxyethyl), 0·64 g., 2-hydroxyethyl. Yields: vinyl 2·22 g., hydroxy-ethyl 0·67 g. Corrected yields: vinyl 64·7%, hydroxyethyl 22·3%. Two duplicate experiments gave vinyl 70·0% and 68·7%, hydroxyethyl 20·0% and 10·0%. Average yields: vinyl 68%, hydroxyethyl 18%.

At least two experiments were carried out with each iodide at each concentration; the results are collected in Table 4.

In one experiment, 2-benzoyloxyethyldimethylsulphonium iodide (2·5 g.), partially dissolved in water (30 ml.), was titrated at 25° with 0·5N-sodium hydroxide (14·8 ml.) at pH *ca.* 10·0. N-Hydrochloric acid (7·4 ml.) was added and the benzoic acid removed with ether; the aqueous layer was freed from dissolved ether and divided into two equal portions. To the first, sodium picrylsulphonate (1·57 g.) in a little water was added; there was immediate deposition of dimethylvinylsulphonium picrylsulphonate (0·93 g., 66%), cream-coloured needles, m. p. 196—198° (decomp.), and a further crop (0·12 g., 9%), m. p. 196—198° (decomp.), was obtained by concentration of the mother-liquor; neither crop showed a depression of m. p. on admixture with authentic material. The second portion was treated with N-sodium hydroxide (5·0 ml.; 1·35 equiv.) and kept overnight at room temperature. N-Hydrochloric acid (5·0 ml.) was added, followed by sodium picrylsulphonate (1·57 g.); concentration yielded 2-hydroxyethyldimethylsulphonium picrylsulphonate (0·80 g., 55%), needles, m. p. and mixed m. p. 167—169°.

TABLE 4. *Fission products of* $R{\cdot}C_6H_4{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^-$ *under titration conditions* (% *yields*).

	0·01M		0·005M			0·01M		0·005M	
R	(II) (%)	(III) (%)	(II) (%)	(III) (%)	R	(II) (%)	(III) (%)	(II) (%)	(III) (%)
H	68	18	72	18	*o*-Me ...	93	0	97	0
o-NO_2 ...	77	12	75	10	*m*-Me ...	73	15	74	10
m-NO_2 ...	8	74	15	82	*p*-Me ...	70	15	87	2
p-NO_2 ...	6	69	8	73	*o*-MeO ...	82	0	82	0
o-Cl	66	3	62	5	*m*-MeO	80	11	82	0
m-Cl	38	52	41	47	*p*-MeO ...	83	0	84	0
p-Cl	—	—	60	20					

(b) *Dimethyl-3-p-nitrobenzoyloxypropylsulphonium iodide.* The iodide (4·0 g., 0·01 mole), partially dissolved in water (60 ml.), was titrated, with stirring, at pH *ca.* 10 with 0·5N-sodium hydroxide (20 ml.); N-hydrochloric acid (10 ml.) was added and the mixture kept overnight. The precipitated solid was identified by mixed m. p. as *p*-nitrobenzoic acid (1·60 g., 96%), m. p. 238—240°; the filtrate was treated with sodium picrylsulphonate (3·15 g.) in a little water. Concentration under reduced pressure yielded two crops of *3-hydroxypropyldimethylsulphonium picrylsulphonate* (2·45 g., 59%), m. p. 155—156° and 153—155°; recrystallisation from methanol gave the pure salt, pale yellow needles, m. p. 155—156°, not depressed on admixture with an authentic specimen (Found: C, 32·3; H, 3·7; N, 10·6. $C_{11}H_{15}O_{10}N_3S_2$ requires C, 32·0; H, 3·6; N, 10·2%). No allyldimethylsulphonium picrylsulphonate could be detected.

(c) *2-Benzoyloxyethyldimethylsulphonium iodide and sodium methoxide.* The iodide (3·4 g.) in methanol was treated, in portions, with sodium methoxide, from sodium (0·23 g.) and methanol (20 ml.). After the mixture had been kept for 30 min., then acidified and filtered, a solution of sodium picrylsulphonate (3·15 g.) in water (25 ml.) was added. The precipitate (2·1 g., 51%) was collected and recrystallised from methanol; *2-methoxyethyldimethylsulphonium picrylsulphonate* forms needles, m. p. 177° (Found: C, 32·8; H, 3·7. $C_{11}H_{15}O_{10}N_3S_2$ requires C, 32·0; H, 3·6%).

Reactions with Alkali added in One Portion.—(a) *2-Benzoyloxyethyldimethylsulphonium iodides.* The iodide (0·01 mole), suspended in water (25 ml.), was treated with N-sodium hydroxide (10·0 ml.), stirred until dissolution was complete, and kept at room temperature for 6 hr. A further quantity (*x* ml.) of N-sodium hydroxide was then added and the mixture kept overnight at room temperature. The solution was then treated with N-hydrochloric acid (10·0 + *x* ml.), and the benzoic acid removed by filtration; sodium picrylsulphonate (3·2 g.), in a little water, was added and any immediate precipitate of bis-2-methylthioethyl ether bismethopicrylsulphonate collected after 5 min.; the filtrate from this was worked up as usual for dimethylvinyl- and 2-hydroxyethyldimethyl-sulphonium picrylsulphonate. The uncorrected yields of the various picrylsulphonates obtained in this way from 2-benzoyloxyethyldimethylsulphonium iodide are recorded in Table 5.

TABLE 5. *Products from* $C_6H_5{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2\}I^-$ *and* NaOH.

Extra NaOH added (*x* ml.)	0·0 *	0·4	0·8	1·2	1·6	2·4 †
(II) (%)	70	21	0	0	0	0
(III) (%)	7	7	11	10	8	9
(IV) (%)	0	54	72	74	73	73

* Mean of 4 experiments. † Mean of 2 experiments.

Bis-2-methylthioethyl ether bismethopicrylsulphonate so obtained crystallised from hot water in pale yellow leaflets, m. p. 215—216° not depressed on admixture with an authentic specimen (p. 1062) (Found: C, 30·6; H, 3·3; N, 11·1. Calc. for $C_{20}H_{24}O_{19}N_6S_4$: C, 30·8; H, 3·1; N, 10·8%). Replacement of sodium picrylsulphonate by sodium picrate in the above experiment yielded *bis-2-methylthioethyl ether bismethopicrate*, yellow needles (from water containing a little ethanol), m. p. 175—176° (Found: N, 12·5. $C_{20}H_{24}O_{15}N_6S_2$ reuires N, 12·9%), while the use of calcium picrate yielded a *calcium picrate compound* of the bismethopicrate, orange needles (from water–ethanol), m. p. 232° (decomp.) (Found: C, 34·6, 34·1; H, 2·1, 2·8; N, 14·0, 13·9. $C_{20}H_{24}O_{15}N_6S_2.C_6H_2O_7N_3Ca_{\frac{1}{2}}$ requires C, 34·6; H, 2·9; N, 14·0%). Either picrate, when shaken with 4N-hydrochloric acid under nitrobenzene, followed by washing of the aqueous layer with ether and evaporation, yielded bis-2-methylthioethyl ether bismethochloride, deliquescent prisms (from anhydrous ethanol–ether), m. p. 196° (decomp.) not depressed on admixture with an authentic specimen (Found: C, 36·0; H, 7·4. Calc. for $C_8H_{19}OS_2Cl_3$: C, 36·0; H, 7·5%). This methochloride (2·65 g.) was refluxed for 3 hr. with sodium iodide (3·5 g.) in acetone (25 ml.). The mixture was concentrated to 15 ml. and the solid rejected; further concentration, followed by several recrystallisations from ethanol, yielded the bismethiodide, m. p. and mixed m. p. 142—143° (decomp.).

In another experiment, the iodide (3·38 g.), in water (50 ml.), was treated with 2N-sodium hydroxide (10·0 ml.). Solution of the iodide was complete after shaking for 2 min. Next morning sodium picrylsulphonate (3·2 g.), in water (40 ml.), was added: dimethylvinylsulphonium picrylsulphonate (2·30 g., 61%) separated in leaflets, m. p. 192° raised by recrystallisation from water to 199°, not depressed on admixture with authentic material.

The following experiments were carried out to demonstrate the interconversions of the various sulphonium compounds in alkali:

(i) *Vinyl into ether.* 2-Benzoyloxyethyldimethylsulphonium iodide (3·38 g.) was stirred for 2½ hr. with water (25 ml.) containing N-sodium hydroxide (10·0 ml.); the solution was divided into two equal portions. The first portion was acidified with N-hydrochloric acid (5·0 ml.), and the precipitated benzoic acid removed by filtration; addition of sodium picrylsulphonate (1·6 g.) to the filtrate yielded dimethylvinylsulphonium picrylsulphonate (1·2 g., 63%), m. p. 193—195° (decomp.) raised to 196—197° (decomp.), not depressed on admixture with authentic material, by recrystallisation from methanol. The second portion was treated with more N-sodium hydroxide (0·4 ml.) and kept overnight; acidification with N-hydrochloric acid (5·4 ml.), removal of benzoic acid by filtration, and addition of sodium picrylsulphonate (1·6 g.) afforded bis-2-methylthioethyl ether bismethopicrylsulphonate (1·4 g., 72%), m. p. and mixed m. p. 208—210°.

(ii) *Vinyl into hydroxyethyl.* The iodide (3·38 g.) was stirred for 2½ hr. with water (25 ml.) and N-sodium hydroxide (10·0 ml.); the solution was acidified with N-hydrochloric acid (10·0 ml.), the benzoic acid removed by filtration, and the filtrate divided into two equal parts. From the first, addition of sodium picrylsulphonate (1·6 g.) precipitated dimethylvinylsulphonium picrylsulphonate (1·1 g., 58%), m. p. 193—195° (decomp.) raised by one recrystallisation from methanol to 196—197° (decomp.), not depressed on admixture with authentic material. N-Sodium hydroxide (5·4 ml.) was added to the second portion which was then kept at room temperature overnight; neutralisation (5·4 ml. of 2N-hydrochloric acid), and addition of sodium picrylsulphonate (1·6 g.), precipitated 2-hydroxyethyldimethylsulphonium picrylsulphonate (1·0 g., 50%), m. p. and mixed m. p. 156—158°.

(iii) *Ether into hydroxyethyl.* The iodide (3·38 g.), in water (25 ml.), was treated with N-sodium hydroxide solution (10·8 ml.), stirred until dissolution was complete (5 min.), and then kept at room temperature overnight; N-hydrochloric acid (10·8 ml.) was then added and benzoic acid removed by filtration. A portion (0·5 ml.) of the filtrate was treated with sodium picrylsulphonate, giving bis-2-methylthioethyl ether bismethopicrylsulphonate, m. p. and mixed m. p. 211—213°. The rest of the filtrate was treated with N-sodium hydroxide (10·8 ml.) and kept for 48 hr. at room temperature. Addition of N-hydrochloric acid (10·8 ml.), followed by sodium picrylsulphonate (3·2 g.), yielded 2-hydroxyethyldimethylsulphonium picrylsulphonate (2·5 g., 63%), m. p. and mixed m. p. 157—158°.

(b) *Dimethyl-3-p-nitrobenzoyloxypropylsulphonium iodide.* The iodide (3·97 g., 0·01 mole), water (70 ml.,) and N-sodium hydroxide (10·0 ml.) were kept at room temperature overnight. Addition of N-hydrochloric acid (10·0 ml.) precipitated *p*-nitrobenzoic acid (1·65 g., 99%; m. p. 238—239°) which was removed by filtration. The filtrate was treated with sodium picrylsulphonate (3·15 g.) and kept at 5° overnight. The golden yellow needles (1·8 g.), m. p. 154°, were collected and a second crop (1·7 g.; total yield, 89%) was obtained by concentration

of the mother-liquor; recrystallisation from methanol yielded 3-hydroxypropyldimethylsulphonium picrylsulphonate, yellow needles, m. p. and mixed m. p. 155°.

(c) 4-*Benzoyloxybutyldimethylsulphonium iodide.* The iodide (1·85 g.) in water (15 ml.) and N-sodium hydroxide (5·0 ml.) was kept for 3 days at 20°. Acidification (5·0 ml. of 2N-hydrochloric acid), removal of benzoic acid by filtration, and addition of sodium picrylsulphonate (1·6 g.) afforded 4-*hydroxybutyldimethylsulphonium picrylsulphonate* (1·5 g., 70%), m. p. 139—141°, which crystallised from methanol in prismatic needles, m. p. 141° (Found: C, 34·0; H, 4·2; N, 9·6. $C_{12}H_{17}O_{10}N_3S_2$ requires C, 33·7; H, 4·0; N, 9·9%).

(d) 2-*Benzoyloxyethyl methyl sulphone.* The sulphone (0·56 g.), suspended in water (10 ml.), was treated with N-sodium hydroxide (2·5 ml.; 1 equiv.), kept overnight at room temperature, and acidified with N-hydrochloric acid (2·5 ml.). After removal of the benzoic acid by ether-extraction, the aqueous layer was evaporated to dryness and the residue extracted with hot chloroform. Concentration of the extract and addition of light petroleum (b. p. 40—60°) yielded bis-2-methylsulphonylethyl ether (0·33 g.) as needles, m. p. 75—77° raised to 78°, not depressed on admixture with authentic material, by recrystallisation from the same solvents (Found: C, 31·5; H, 6·3. Calc. for $C_6H_{14}O_5S_2$: C, 31·3; H, 6·1%).

(e) 2-Benzoyloxyethyl methyl sulphoxide was recovered unchanged after treatment with sodium hydroxide in the manner described for the sulphone.

(f) *Dimethyl-2-phenoxyethylsulphonium iodide.* The iodide (3·1 g.; Crane and Rydon, *loc. cit.*) was suspended in water (50 ml.) and treated with N-sodium hydroxide (10 ml.). Next morning N-hydrochloic acid (10·0 ml.) was added and phenol extracted with ether. Addition of sodium picrylsulphonate to the aqueous layer afforded an immediate precipitate of bis-2-methylthioethyl ether bismethopicrylsulphonate (2·7 g., 69%), orange needles, m. p. and mixed m. p. 213—214°. Concentration of the mother-liquor yielded dimethylvinylsulphonium picrylsulphonate (0·25 g., 7%), m. p. 192—194° raised to m. p. and mixed m. p. 199—200° by recrystallisation from water.

(g) 2-*Benzoyloxyethyltrimethylammonium iodide.* The iodide (3·35 g.), N-sodium hydroxide (10·0 ml.), and water (30 ml.) were kept at room temperature for 3 days. Addition of N-hydrochloric acid (10·0 ml.) precipitated benzoic acid (1·05 g., 86%), which was removed by filtration. Addition of sodium picrylsulphonate (3·1 g.) to the filtrate precipitated *choline picrylsulphonate* (2·8 g., 71%), m. p. 234—244° (decomp.), raised to m. p. and mixed m. p. 244° (decomp.) by recrystallisation from methanol (Found: N, 14·1. $C_{11}H_{16}O_{10}N_4S$ requires N, 14·1%).

(h) *Dimethyl-2-p-nitrobenzoyloxyethylammonium iodide.* The iodide (1·9 g.), N-sodium hydroxide (5·0 ml.), and water (30 ml.) were kept at room temperature for 3 days. Unchanged starting material (0·07 g.) was removed by filtration; acidification of the filtrate with N-hydrochloric acid (5·0 ml.) precipitated *p*-nitrobenzoic acid (0·75 g., 94%), which was removed by filtration. Addition of sodium picrylsulphonate (1·4 g.) then precipitated choline picrylsulphonate (1·1 g., 55%), m. p. 235—240° (decomp.).

Action of more than One Equivalent of Alkali.—(a) 2-*Aroyloxyethyldimethylsulphonium iodides.* The iodide (0·01 mole), in water (10—40 ml.) containing N-sodium hydroxide (20 ml.), was heated to 95—100° in a slow stream of nitrogen. The effluent gases were led up a short column and passed through a trap cooled to −30° into a tube containing cuprous chloride–hydroxylamine. The contents of the cold trap were treated with a solution of mercuric chloride (2·5 g.) in ethanol (25 ml.); colourless prisms of dimethyl sulphide–mercuric chloride complex, m. p. and mixed m. p. 150—152°, were deposited. Acidification of the alkaline reaction mixture precipitated the benzoic acid which was collected and weighed. 2-Benzoyloxy-, 2-*m*-nitrobenzoyloxy-, and 2-*o*-toluoyloxy-ethyldimethylsulphonium iodides all gave acetylene, dimethyl sulphide (50, 49, and 64% yield), and the benzoic acid (87, 71, and 82% yield); similar results were obtained when the first equivalent of alkali was added slowly in the cold.

(b) 2-*Benzoyloxyethyltrimethylammonium iodide.* Under the above conditions no acetylene was produced and there was only a faint smell of trimethylamine; acidification of the residue afforded a theoretical yield of benzoic acid and treatment with sodium picrylsulphonate gave choline picrylsulphonate, m. p. and mixed m. p. 244° (decomp.).

(c) *Picrylsulphonates.* Under the same conditions, the following picrylsulphonates afforded dimethyl sulphide, isolated and identified as the mercuric chloride complex and as the sulphidimine, in the yields indicated: dimethylvinylsulphonium (80%); 2-hydroxyethyldimethylsulphonium (84%); bis-2-methylthioethyl ether (70%).

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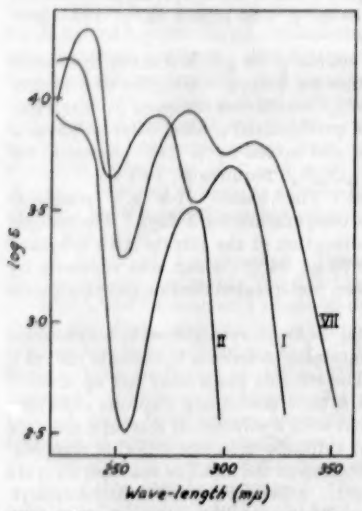
The Constitution of Homolycorine and Lycorenine.

By T. Kitagawa, W. I. Taylor, S. Uyeo, and H. Yajima.

[Reprint Order No. 5872.]

Homolycorine has been shown to be an *N*-methyl tertiary base containing a δ-lactone grouping and to give deoxylycorenine on lithium aluminium hydride reduction followed by treatment with acid. Lycorenine, which has a cyclic hemiacetal moeity, was converted into homolycorine either by oxidation or by disproportionation in alkali. From these and other results structures have been assigned to both alkaloids.

Twenty-five years ago Kondo and Tomimura (*J. Pharm. Soc. Japan*, 1929, **49**, 438) isolated from the alkaloids of *Lycoris radiata* Herb. a base, homolycorine, m. p. 175°, whose isolation was facilitated by the solubility of its hydrochloride in chloroform. Homolycorine, to which the formula $C_{19}H_{23}O_4N$ was ascribed, contained 2 methoxyl groups and also an *N*-methyl group. At that time the above authors placed little value on the latter determination because in their hands lycorine which has a bridgehead nitrogen atom also gave an apparent *N*-methyl content by the macro-method of Herzig and Meyer. Kolle and Gloppe later (*Pharm. Zentralhalle*, 1934, **75**, 237) extracted from the bulbs of *Narcissus poeticus* a base of m. p. 172°, very similar to homolycorine but named by them narcipoetine in case it was not identical with homolycorine. Very recently Boit (*Chem. Ber.*, 1954, **87**, 681) announced the separation from *Leucojum vernum* L. as well as from *Narcissus poeticus* var. *ornatus* of an alkaloid whose properties were almost identical with those recorded for homolycorine except in the empirical formula and specific rotation. Dr. H. G. Boit has now shown by direct comparison that his compounds are identical with the original sample of homolycorine (Dr. H. Kondo, personal communication).



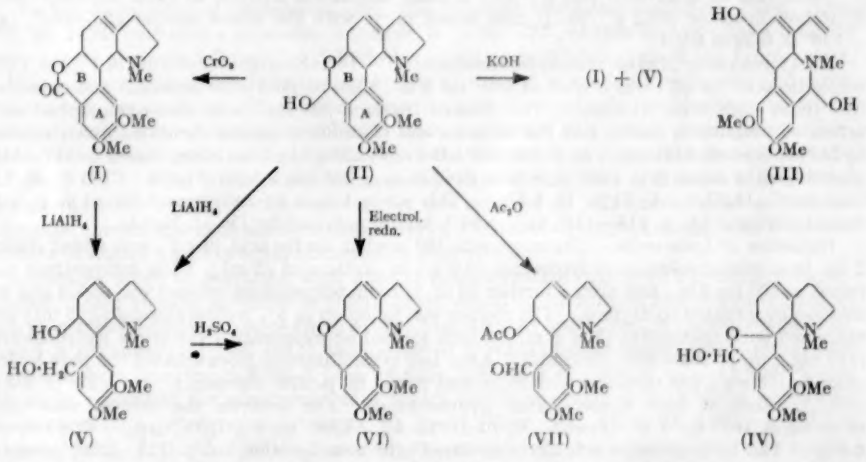
Ultra-violet absorption of (I) *homolycorine*, (II) *lycorenine, and* (VII) *acetyl-lycorenine, all in* 95% EtOH.

We have independently confirmed the formula $C_{18}H_{21}O_4N$ as assigned by Boit (*loc. cit.*) and also the fact that besides the two methoxyl groups there is one *N*-methyl group. While homolycorine was reported by Kondo and Tomimura (*loc. cit.*) to give a diacetyl derivative, m. p. 173°, we have been unable to confirm this, the base being always recovered unchanged after attempted acetylation, so that the nature of two oxygen atoms still remained to be elucidated. It was found that although the base was insoluble in cold sodium carbonate or sodium hydroxide solution it dissolved in hot sodium hydroxide to yield a salt which could not be extracted from aqueous solutions by organic solvents; after acidification of the alkaline solution homolycorine was isolated as its hydrochloride in quantitative yield. Thus the two oxygen atoms were present in a lactone. Both the infra-red (ν_{CO} 1712 cm.$^{-1}$) and the ultra-violet absorption spectrum (curve I) of the alkaloid were consistent with a partial structure indicated by rings A and B of formula (I), which contain a veratroyl residue and a δ-lactone grouping. δ-Lactones have carbonyl stretching frequencies in the same position as the corresponding open-chain esters, in this case at *ca.* 1720 cm.$^{-1}$ (Rasmussen and Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1073); γ-lactones absorb at much higher frequencies, *e.g.*, the methoxyphthalides have ν_{CO} 1750 cm.$^{-1}$ (Duncanson, Grove, and Zealley, *J.*, 1953, 1331).

Reduction of homolycorine by lithium aluminium hydride gave tetrahydrohomolycorine,

$C_{18}H_{25}O_4N$, m. p. 154°, which with hot dilute sulphuric acid afforded anhydrotetrahydrohomolycorine, $C_{18}H_{23}O_3N$, m. p. 117—118°. The latter compound was identical with deoxylycorenine, m. p. 117—118°, obtained by Kondo and Ikeda (*Ann. Report ITSUU Lab.*, 1952, **3**, 55) on electrolytic reduction of lycorenine, a base also isolated from *Lycoris radiata* (Kondo, Tomimura, and Ishiwata, *J. Pharm. Soc. Japan*, 1932, **52**, 433; Kondo and Mitsuhashi, *ibid.*, 1934, **54**, 1001; Kondo and Ikeda, *Ber.*, 1940, **73**, 867). The close relation between the two alkaloids was further demonstrated by the following experiments. Reduction of lycorenine with lithium aluminium hydride yielded tetrahydrohomolycorine, and although lycorenine was stable to potassium ferricyanide it was readily oxidised by chromic acid to homolycorine. Finally, as expected, with hot alcoholic potassium hydroxide lycorenine underwent disproportionation to homolycorine and tetrahydrohomolycorine. Lycorenine must therefore have the cyclic hemiacetal structure shown in rings A and B of formula (II). The results of the last experiment suggest that homolycorine could actually be produced from lycorenine during the isolation procedure.

On the basis of their extensive investigations into the chemistry of lycorenine Kondo and Ikeda (*loc. cit.*, 1952) put forward as working hypothesis the structure (III) for the alkaloid. Wenkert and Hansen (*Chem. and Ind.*, 1954, 1262) after a re-analysis of Kondo's



data and biogenetic considerations have suggested formula (IV). While we are essentially in agreement with the general correctness of Wenkert and Hansen's formula it can be criticized on the grounds that in a number of degradation product of lycorenine the potential tertiary benzylic hydroxyl group should have been eliminated, *e.g.*, on acetylation of lycorenine. It is clear from our results that the cyclic hemiacetal ring in lycorenine must be six-membered, leading to (II) as the formula. Thus homolycorine, tetrahydrohomolycorine, and deoxylycorenine are (I), (V), and (VI) respectively.

Lycorenine (ultra-violet spectrum, curve II) on acetylation yields (VII) as indicated by the ultra-violet absorption spectrum (curve VII) (which is very similar to that of veratraldehyde) rather than the acetate of the hemiacetal form. Further aspects of the chemistry of lycorenine and a discussion of Wenkert's newer biogenetic scheme for *Amaryllidaceae* alkaloids will be presented later.

Experimental

Absorption spectra were taken in 95% ethanol.

Homolycorine.—Homolycorine was crystallized from water to constant m. p. 175°, $[\alpha]_D$ +85° (*c*, 0·43 in EtOH), ν_{CO} 1712 cm.$^{-1}$, $\lambda_{max.}$ 225, 267, and 305 mμ (log ε 4·18, 3·91, and 3·69) (Found: C, 68·5; H, 6·6; N, 4·4; OMe, 19·6; NMe, 4·0. Calc. for $C_{18}H_{21}O_4N$: C, 68·6; H, 6·7; N, 4·5; 2OMe, 19·7; NMe, 4·8%). The *hydrochloride* had m. p. 278° (decomp.), $[\alpha]_D$ +100°

(*c*, 0·5 in H_2O; dried sample), $[\alpha]_D$ +15° (*c*, 0·33 in $CHCl_3$; dried sample), $\lambda_{max.}$ 227, 270, 301 mμ (log ε 4·21, 3·94, 3·77) (Found, after being dried at 105° for 6 hr.: C, 61·7; H, 6·3. $C_{18}H_{21}O_4N$,HCl requires C, 61·5; H, 6·3%).

Treatment of Homolycorine with Alkali.—Homolycorine (0·1 g.) was dissolved in hot aqueous sodium hydroxide (8 ml.; 5%), then heated on a water-bath for 2 hr. After cooling, homolycorine could not be induced to crystallize nor could it be extracted from the aqueous alkaline solution by ether, benzene, or chloroform. After acidification (HCl), the chloroform extract was evaporated to dryness to yield homolycorine hydrochloride (90 mg.), m. p. and mixed m. p. 278° (decomp.).

Tetrahydrohomolycorine.—Homolycorine (0·2 g.) and lithium aluminium hydride (0·2 g.) were refluxed in dry ether for 7 hr. After addition of ice-water and filtration the ethereal solution was evaporated to dryness and chromatographed over aluminium oxide. After elution first with benzene, the ethanol eluate yielded *tetrahydrohomolycorine* (plates from acetone) (140 mg.), m. p. 154·5°, $[\alpha]_D$ −101° (*c*, 0·33 in EtOH), $\lambda_{max.}$ 281 mμ (log ε 3·45) (Found: C, 67·7; H, 7·9. $C_{18}H_{25}O_4N$ requires C, 67·6; H, 7·9%). The diacetate had m. p. 133—134° (from ether–light petroleum) (Found: C, 65·7; H, 7·1; N, 3·6; Ac, 21·3. Calc. for $C_{22}H_{29}O_6N$: C, 65·5; H, 7·3; N, 3·5; 2Ac, 21·3%) and was identical with the so-called acetyldeoxylycorenine described by Kondo and Ikeda (*loc. cit.*, 1952).

Reduction of lycorenine (0·5 g.) with lithium aluminium hydride in ether afforded tetrahydrohomolycorine (0·32 g.), m. p. and mixed m. p. with the above sample 153—155°, $[\alpha]_D$ −106° (*c*, 0·39 in EtOH).

Deoxylycorenine (*Anhydrotetrahydrohomolycorine*).—Tetrahydrohomolycorine (0·1 g.) in 1·5% sulphuric acid (15 ml.) was heated at 100° for 2 hr., then basified with ammonia and extracted five times with ether (10 ml.). The ethereal extract (80 mg.) was chromatographed over activated aluminium oxide, and the benzene and chloroform eluates furnished anhydrotetrahydrohomolycorine (40 mg.), m. p. 94—99° after crystallisation from ether, raised to 117—118° after drying *in vacuo*, $[\alpha]_D$ +95° (*c*, 0·65 in EtOH), $\lambda_{max.}$ 285 (log ε 3·52) (Found: C, 71·6; H, 7·5. Calc. for $C_{18}H_{23}O_3N$: C, 71·7; H, 7·7%). This product gave an undepressed mixed m. p. with deoxylycorenine (m. p. 118—119°, $[\alpha]_D$ +91°), kindly provided by Dr. H. Kondo.

Oxidation of Lycorenine.—Chromic oxide (80 mg.) in acetic acid (9 ml.) was added during 2 hr. to a stirred solution of lycorenine (0·2 g.) in acetic acid (5 ml.). The temperature was raised to 40° for 3 hr., and after a further 12 hr. at room temperature ethanol was added and the solution evaporated to dryness. The residue was taken up in 3% hydrochloric acid (8 ml.) and extracted with chloroform (3 × 8 ml.), which yielded on evaporation the crude hydrochloride (120 mg.), m. p. 262—268° (decomp.). After two crystallizations from ethanol the pure hydrochloride (78 mg.) was obtained with m. p. and mixed m. p. 278° (decomp.), $[\alpha]_D$ +23° (*c*, 2·3 in $CHCl_3$), identical with homolycorine hydrochloride. For analysis the sample was dried *in vacuo* at 105° for 6 hr. (Found: C, 61·1; H, 6·1. Calc. for $C_{18}H_{21}O_4N$,HCl: C, 61·4; H, 6·3%). The hydrochloride was also converted into homolycorine, m. p. 173—175°, identical with authentic material. Lycorenine (42 mg.) was recovered from the above aqueous solution after basification and extraction with chloroform.

Lycorenine was recovered in 75% yield after attempted oxidation in aqueous alkaline potassium ferricyanide solution.

Disproportionation of Lycorenine.—Lycorenine (0·3 g.) and potassium hydroxide (4 g.) in ethanol (20 ml.) were refluxed for 8 hr., then, after removal of the ethanol, water (35 ml.) was added and the solution extracted 4 times with chloroform (6 ml.). The chloroform extract afforded a residue (0·18 g.) which after chromatography over activated aluminium oxide gave from the benzene eluate a product (78 mg.), m. p. 197—199° alone or mixed with lycorenine, and from the chloroform eluate a compound (34 mg.), m. p. 153—154° alone or mixed with tetrahydrohomolycorine. The aqueous solution was acidified (HCl) and extracted with chloroform (4 × 6 ml.), to yield homolycorine hydrochloride (100 mg.), m. p. 276° (decomp.), which gave the free base, m. p. 173—175° alone or in admixture with homolycorine.

Acetyl-lycorenine.—The acetyl derivative prepared by acetylation of lycorenine (Kondo and Ikeda, *loc. cit.*, 1952) had $\lambda_{max.}$ 235, 281, and 313 (log ε 4·31, 3·95, 3·81).

We thank Dr. H. Kondo for his interest and for the gift of the alkaloids used in this work, also Mr. W. Fulmor and staff of Lederle Laboratories Division of the American Cyanamid Corporation for infra-red spectra.

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Chemical Laboratories, University of New Brunswick. [*Received, November 11th*, 1954.]

Conjugated Acids from Castor Oil. Octadeca-9 : 11-dienoic Acid and Octadec-11-en-9-ynoic Acid (Ximenynic or Santalbic Acid).

By James Grigor, D. M. MacInnes, John McLean, and (in part) A. J. P. Hogg.

[Reprint Order No. 5873.]

Ximenynic acid has been prepared from castor oil. The acid thus prepared is identical with the natural acid and also with santalbic acid.

Castor oil has been dehydrated by use of a variety of catalysts (Forbes and Neville, *Ind. Eng. Chem.*, 1940, **32**, 535), the extent of conjugated dienic esters formed being around 30% (Grummit and Gleming, *ibid.*, 1945, **37**, 485). The acids present have been investigated by Priest and von Mikusch (*ibid.*, 1940, **32**, 1314), who have shown that octadeca-9 : 12-dienoic acid is present in greater quantity than the isomeric 9 : 11-dienoic acid. Mangold (*Monatsh.*, 1894, **15**, 307) prepared *trans-trans*-octadeca-9 : 11-dienoic acid, m. p. 54°, by the distillation of ricinelaidic acid, and Schmidt and Lehmann (*Helv. Chim. Acta*, 1939, **33**, 1494) prepared a geometrical isomer, m. p. 32—33°, of this acid by allylic bromination of methyl oleate followed by dehydrobromination and hydrolysis of the bromo-ester.

While investigating the dehydrating action of thionyl chloride on ricinoleic and ricinelaidic esters, we find that chlorination occurs to give the unstable 12-chloro-esters, which undergo partial loss of hydrogen chloride when subjected to vacuum distillation. Subsequent dehydrohalogenation and hydrolysis of the chloro-esters with alkali gives Mangold's acid, m. p. 54°. If in place of the pure methyl esters, castor oil is treated with thionyl chloride, and the resulting chloroglycerides are refluxed or autoclaved with potassium hydroxide, the unsaturated acids produced may be distilled as methyl esters, and from the distillate Mangold's acid is again obtained on hydrolysis.

A parallel series of reactions with methyl ricinstearolate (methyl 12-hydroxyoctadec-9-ynoate) again yielded an unstable chloro-ester, which on hydrolysis and dehydrohalogenation gave *trans*-octadec-11-en-9-ynoic acid. The infrared spectrum (in carbon disulphide) showed a maximum at 955 cm.$^{-1}$ indicative of a *trans*-olefinic bond, while ultraviolet absorption data [maximum 2290 Å ($\varepsilon = 16{,}610$), inflection at 2400 Å ($\varepsilon = 12{,}200$)] agree with those published for ximenynic acid, which has been obtained from three species of *Ximenia* genus (Ligthelm and Schwartz, *J. Amer. Chem. Soc.*, 1950, **72**, 1868; Ligthelm and von Holdt, *J.*, 1952, 1088). Moreover, the melting points of our material, its amide, and *p*-bromophenacyl ester agree with the values for the natural acid and the corresponding derivatives.

Ximenynic acid is the major component of the seed fats of two Australian members of the *Santalaceae* (Hatt and Szumer, *Chem. and Ind.*, 1954, 962), and these authors have suggested that "santalbic acid," $C_{18}H_{30}O_2$, obtained by Madhuraneth and Manjunath (*J. Indian Chem. Soc.*, 1938, **15**, 389) from the seed fat of the sandalwood tree, *Santalum album*, Linn., will probably prove to be identical with ximenynic acid. In a preliminary note (*Chem. and Ind.*, 1954, 1112), we have shown that our ximenynic acid is in fact identical with "santalbic acid" obtained by Gunstone and McGee (*ibid.*, p. 1112). Oxidation of synthetic *trans*-octadec-11-en-9-ynoic acid according to the method of Swern *et al.* (*J. Amer. Chem. Soc.*, 1951, **73**, 2730) gave 11 : 12-dihydroxyoctadec-9-ynoic acid), identical with the product obtained by Gunstone and McGee (*loc. cit.*) from "santalbic acid." Hydrogenation of the dihydroxyacetylenic acid gave 11 : 12-dihydroxystearic acid, m. p. 128—129°. Huber (*J. Amer. Chem. Soc.*, 1951, **73**, 2730) has prepared 11 : 12-dihydroxystearic acids, m. p.s 95—96° and 129—130°, from the corresponding *cis*- and *trans*-ethylenic acids, hence the *trans*-configuration of the olefinic bond in ximenynic acid is confirmed. The infrared spectrum of the synthetic acid is identical with that of "santalbic acid" (Gunstone and McGee, *loc. cit.*), moreover both acids give identical *p*-bromophenacyl esters, and both have been hydroxylated to identical dihydroxystearolic acids.

Experimental

Ultraviolet spectra were determined in ethanol on a Unicam SP. 500 spectrophotometer, and infrared spectra were obtained in carbon disulphide on a Perkin-Elmer double-beam instrument.

Methyl 12-*Chloro-oleate.*—Thionyl chloride (40 g.) was added slowly to methyl ricinoleate (40 g.) at 0° with occasional shaking, and the mixture left at room temperature overnight. Excess of thionyl chloride was removed, the residue dissolved in ether, and the solution washed with sodium carbonate solution and water, and dried (Na_2SO_4). Removal of ether gave *methyl* 12-*chloro-oleate* (23 g.), b. p. 158—163°/0·18 mm. (Found: C, 69·5; H, 10·9; Cl, 8·7. $C_{19}H_{35}O_2Cl$ requires C, 69·0; H, 10·7; Cl, 10·7%). Redistillation of the ester is accompanied by loss of hydrogen chloride.

Methyl 12-*Chloroelaidate.*—Prepared as above from methyl ricinelaidate, the 12-chloro-compound had b. p. 155—157°/10^{-3} mm. (Found: C, 68·9; H, 10·7; Cl, 10·1%).

Octadeca-9 : 11-*dienoic Acid.*—(*A*) Methyl 12-chloroelaidate (10 g.) in ethanol (200 ml.) was refluxed with potassium hydroxide (10 g.) in water (10 c.c.) for 10 hr. On acidification, a clear oil (7·5 g.) separated, which was extracted, washed, and stored at 0°, and then deposited octadeca-9 : 11-dienoic acid, m. p. 53—54° alone or mixed with a specimen prepared according to Mangold (*loc. cit.*). Light absorption: Max. 2320 Å; $\varepsilon = 32{,}000$.

(*B*) *From castor oil.* Thionyl chloride (52·5 g.) was added slowly to castor oil (100 g.) with occasional shaking, and the mixture left overnight. Removal of excess of thionyl chloride left a dark red oil which was washed in ethereal solution with sodium carbonate (5%) and water. Removal of ether left a red oil (94·5 g.) which was refluxed with potassium hydroxide (50 g.) in ethanol (400 ml.) for 24 hr. The mixture was poured into water and acidified. Isolation gave a mixture of acids containing 47·5% of conjugated diene. [A second run in which the mixed glycerides were hydrolysed at 180° for 6 hr. gave crude acids containing 54% of conjugated diene (light absorption: Max. 2300 Å; $\varepsilon = 17{,}150$).] The mixed acids were esterified to give methyl esters, b. p. 128—132°/2 × 10^{-3} mm. Hydrolysis of the esters (35 g.) with sodium hydroxide (2N; 90 ml.) in methanol (160 ml.) followed by extraction with ether gave an oil (24·5 g.) which slowly deposited crude acid, m. p. 37—46°. Recrystallization from methanol gave octadeca-9 : 11-dienoic acid, m. p. 53—54° undepressed when mixed with an authentic sample. Light absorption: Max. 2320 Å ($\varepsilon = 32{,}500$).

(*C*) Similar treatment of methyl 12-chloro-oleate also produced Mangold's acid, m. p. 53—54°.

Octadeca-9 : 11-*dienoamide.*—Prepared from methyl octadeca-9 : 11-dienoate and liquid ammonia in an autoclave at 150° for 15 hr., the *amide* had m. p. 98—99° (Found: C, 77·2; H, 11·6; N, 4·9. $C_{18}H_{33}ON$ requires C, 77·4; H, 11·8; N, 5·0%). Light absorption: Max. 2300 Å ($\varepsilon = 32{,}000$). The amide was also obtained from methyl 12-chloro-oleate and liquid ammonia at 160° for 15 hr. The S-*benzylthiuronium salt* formed needles, m. p. 127—129°, from alcohol (Found: C, 70·3; H, 9·6. $C_{26}H_{42}O_2N_2S$ requires C, 70·0; H, 9·4%).

Ricinstearolic Acid.—The following modification of Mühle's method (*Ber.*, 1913, **46**, 2096) was employed. To castor oil (200 g.) in ethyl alcohol (100 g.) at −30°, bromine was added in a thin stream with stirring. When addition was complete, the product was refluxed for 10 hr. with potassium hydroxide (240 g.) in water (160 g.). The mixture was poured into water (1·2 l.), acidified with sulphuric acid (5N), and set aside overnight. The hard cake of crude acid was removed and dissolved in ether, and the solution dried (Na_2SO_4). Removal of ether gave ricinstearolic acid (142 g.) as plates from light petroleum (b. p. 40—60°), m. p. 49—50°.

Methyl Ricinstearolate.—Prepared from the acid (36·5 g.) and isolated in the uusal way, the ester (24 g.) had m. p. 19—20°, b. p. 148—150°/2 × 10^{-3} mm. Mühle (*loc. cit.*) describes the ester as a liquid, b. p. 225°/12 mm.

Octadec-11-*en*-9-*ynoic Acid.*—Freshly purified thionyl chloride (40 g.) was added dropwise with stirring to methyl ricinstearolate (85 g.) at −10°. After addition was complete, stirring was continued for 2 hr., and the mixture left overnight at room temperature. Excess of thionyl chloride was removed under reduced pressure, and an ethereal solution of the residue was washed with water, sodium carbonate solution, and water, and dried (Na_2SO_4). The residue (86 g.) of crude methyl 12-chlorostearolate was refluxed with ethanolic potash (15%; 280 c.c.) for 24 hr., and the mixture poured into water, acidified, and extracted with ether. Removal of ether gave a fraction (41 g.), b. p. 198/7·5 × 10^{-3} mm. Several crystallizations from acetone (10 c.c./g.) at −25°, followed by crystallization from light petroleum (b. p. 40—60°) at −10° gave *octadec*-11-*en*-9-*ynoic acid* (34 g.), m. p. 38—39° alone and when mixed with a specimen of "santalbic acid" (Found: C, 77·3; H, 10·7. $C_{18}H_{30}O_2$ requires C, 77·7; H, 10·9%). Light

absorption: Max. 2290 Å (ε = 16,610); inflection at 2400 Å (ε = 12,200). Infrared absorption peak at 955 cm.$^{-1}$ (*trans*-olefinic bond). The infrared absorption curve was identical with that obtained from "santalbic acid." The p-*bromophenacyl ester* formed needles, m. p. 54°, from alcohol and did not depress the m. p. of the *p*-bromophenacyl ester of santalbic acid (Found: C, 65·4; H, 7·6. $C_{26}H_{33}O_3Br$ requires C, 65·7; H, 7·4%).

Octadec-11-en-9-ynoamide.—The methyl ester (980 mg.) in ethanol (20 ml.) was heated with liquid ammonia (70 ml.) in a sealed tube at 75° for 24 hr. Isolation in the usual way gave *octadec-11-en-9-ynoamide* (690 mg.), m. p. 105°, as needles (from aqueous methanol) (Found: C, 78·0; H, 11·0. $C_{18}H_{31}ON$ requires C, 77·8; H, 11·3%).

11 : 12-*Dihydroxystearolic Acid.*—Octadec-11-en-9-ynoic acid (2·8 g.) in formic acid (98%; 30 ml.) and hydrogen peroxide (30%; 1·6 ml.) was stirred at 50° for 1½ hr. Isolation in the usual manner and crystallization from ether–petroleum, initially at −20° and then at room temperature, gave 11 : 12-dihydroxystearolic acid (1·9 g.) as plates, m. p. 89—90° alone and when mixed with a specimen prepared by Dr. Gunstone (*loc. cit.*) from "santalbic acid" (Found: C, 69·0; H, 10·2. Calc. for $C_{18}H_{32}O_4$: C, 69·2; H, 10·3%).

11 : 12-*Dihydroxystearic Acid.*—11 : 12-Dihydroxystearolic acid (95 mg.) in ethyl acetate–acetic acid (5 : 1; 30 ml.) was shaken in hydrogen with platinum (20 mg.) for 2 hr. Isolation in the usual manner gave 11 : 12-dihydroxystearic acid (70 mg.), m. p. 128—129°, as plates from ethanol. Huber (*loc. cit.*) records m. p. 129—130°.

Stearic Acid.—Complete hydrogenation of octadec-11-en-9-ynoic acid gave stearic acid, m. p. and mixed m. p. 69—70°.

The authors express grateful acknowledgment to Dr. F. D. Gunstone for helpful discussion and specimens of santalbic acid and derivatives, to Professor Spring, F.R.S., for his interest and encouragement, to Dr. G. D. Meakins for the infrared spectra, and to the Cross Trust for scholarships (to J. G. and D. M. McI.).

The Royal Technical College, Glasgow, C.1. [*Received, November 11th*, 1954.]

Potential Thiophen Chemotherapeutics. Part IV. The Thiophen Analogues of* p-*Acetamidobenzaldehyde Thiosemicarbazone and Sulphanilamide.*

By J. Cymerman-Craig and D. Willis.

[Reprint Order No. 5889.]

Formylation of 2-acetamidothiophen (whose preparation from methyl 2-thienyl ketoxime is improved) gave 2-acetamido-5-formylthiophen, the structure of which was rigidly proved by an alternative synthesis from 2-formylthiophen.

2-Phthalimidothiophen was converted into 5-phthalimidothiophen-2-sulphonamide. On attempted hydrolysis, both these compounds either resisted hydrolysis or underwent ring fission, but the analogous 4-phthalimidobenzenesulphonamide was hydrolysed normally.

In view of the tuberculostatic properties of thiosemicarbazones of aromatic and heterocyclic aldehydes, notably *p*-acetamidobenzaldehyde thiosemicarbazone (Behnisch, Mietzsch, and Schmidt, *Angew. Chem.*, 1948, **60**, 113; Hoggarth, Martin, Storey, and Young, *Brit. J. Pharmacol.*, 1949, **4**, 248), it was of interest to prepare the thiophen isostere of this compound.

2-Acetamidothiophen has been obtained by acetylation of the unstable 2-aminothiophen (Steinkopf, *Annalen*, 1914, **403**, 17; Lew and Noller, *J. Amer. Chem. Soc.*, 1950, **72**, 5715), and the Schmidt reaction on methyl 2-thienyl ketone gave a mixture of 2-acetamidothiophen and the isomeric *N*-methyl-2-thenoylamine (Hurd and Moffat, *J. Amer. Chem. Soc.*, 1951, **73**, 613). The Beckmann rearrangement of the more accessible methyl 2-thienyl

* Part III, *J.*, 1954, 237.

ketoxime with phosphorus pentachloride has been reported by Steinkopf and by Hurd and Moffat (*locc. cit.*) to give very poor yields of amide. Repetition of Steinkopf's procedure gave 5—10% of amide until it was found that 2-acetamidothiophen was readily soluble in the cold at pH 1, but insoluble above pH 2. It was thus not extracted from the acid media resulting from the hydrolysis of phosphorus pentachloride, but by buffering the solution to pH 5—6 before extraction, the yield was readily raised to 55%. Similar solubility has been observed with 2-acetamidomethylthiophen (Cymerman and Faiers, *J.*, 1952, 165) and 5-acetamidomethylthiophen-2-sulphonic acid (Cymerman-Craig and Loder, *J.*, 1954, 237).

Attempts to carry out the Beckmann rearrangement of methyl 2-thienyl ketoxime with agents other than phosphorus pentachloride failed (cf. Hurd and Moffat, *loc. cit.*). Ethereal hydrogen chloride left the oxime unchanged, while hydrogen chloride in acetic anhydride (Beckmann, *Ber.*, **1887**, **20**, 2581) gave the stable oxime acetate.

Reaction of 2-acetamidothiophen with *N*-methylformanilide and phosphorus oxychloride (1—3 mols.) at 0—5° by King and Nord's method (*J. Org. Chem.*, **1948**, **13**, 635) gave an oil containing 45—69% of the desired 2-acetamido-5-formylthiophen (estimated as the semicarbazone); although its pure derivatives were readily obtained from the oily product, the pure aldehyde was obtained only by carrying out the reaction at 0—5° in dimethylformamide (74% yield) (cf. *Chem. and Ind.*, 1953, 797).

2-Acetamido-5-formylthiophen thiosemicarbazone was tested against *Mycobacterium tuberculosis* H37Rv by Professor S. D. Rubbo who reports it to be active *in vitro* at a concentration of M/512,000 in Youman's medium, in the presence or absence of 10% of serum.

Attempted regeneration of the aldehyde from its semicarbazone (Kon, *J.*, 1930, 1616) failed with both 2% and 10% sulphuric acid at room temperature, while more vigorous conditions gave evidence of hydrolysis of the acetamido-group. Its structure was proved by an alternative synthesis from 2-formylthiophen. The aldehyde diacetate was obtained in 78% yield by a modification, using anhydrous zinc chloride as catalyst, of Patrick and Emerson's method (*J. Amer. Chem. Soc.*, 1952, **74**, 1356), which employed stannous chloride and gave a low yield in our hands. These authors nitrated the aldehyde diacetate, and proved the structure of the 5-nitro-aldehyde diacetate by hydrolysis, oxidation, and conversion into the known methyl 5-nitro-2-thenoate. The nitro-aldehyde diacetate was subjected to reductive acetylation with iron and acetic anhydride in acetic acid, the product (after brief acid hydrolysis) giving crystalline derivatives identical with those of 2-acetamido-5-formylthiophen obtained previously.

After this work had been completed, Campaigne and Archer (*J. Amer. Chem. Soc.*, 1953, **75**, 989) reported the synthesis of 2-acetamido-5-formylthiophen in 47% yield from 2-acetamidothiophen and dimethylformamide alone at elevated temperatures, and also prepared its thiosemicarbazone (Campaigne, Monroe, Arnwine, and Archer, *ibid.*, p. 988). These authors also claim a proof of structure of the aldehyde by oxidation to the corresponding acid, m. p. 271—272°, but the configuration of this acid has not been definitely settled: it is described by Steinkopf and Muller (*Annalen*, 1926, **448**, 210) as 4-acetamido-2-thenoic acid, and was obtained by these authors from a nitro-2-thenoic acid which gave both 2- and 3-nitrothiophen on decarboxylation and was shown later by Rinkes (*Rec. Trav. chim.*, 1932, **51**, 1134) to consist of 5-nitro-2-thenoic acid accompanied by the 4-nitro-isomer. Since our 2-acetamido-5-formylthiophen was identical with that of Campaigne and Archer (*loc. cit.*), the alternative synthesis from 2-formylthiophen described above also proves that Steinkopf and Muller's acid, m. p. 271—272°, was in fact the 5-isomer.

The preparation of 2-aminothiophen-5-sulphonamide, the thiophen analogue of sulphanilamide, has been attempted by a number of workers. Nitration of thiophen-2-sulphonyl chloride (Burton and Davy, *J.*, **1948**, 525) and chlorosulphonation of 2-nitrothiophen (Lew and Noller, *loc. cit.*) gave only 5-aminothiophen-3-sulphonamide; chlorosulphonation of 2-acetamidothiophen (Lew and Noller, and Hurd and Moffat, *locc. cit.*) afforded only a disulphonyl chloride; and attempted conversion of 5-acetamidothiophen-2-sulphonic acid (Hurd and Priestley, *J. Amer. Chem. Soc.*, 1947, **69**, 859) into the sulphonyl chloride proved abortive (cf. Dann and Moller, *Chem. Ber.*, 1947, **80**, 23).

Re-investigation confirmed that chlorosulphonation of 2-acetamidothiophen at temperatures between −5° and 50° gave only sulphonic acids, while the action of sulphuryl chloride, reported to act as both chlorinating and chlorosulphonating agent (Tohl and Eberhard, *Ber.*, 1893, **26**, 2940; Boeseken, *Rec. Trav. chim.*, 1911, **30**, 382), on the same compound gave 2-acetamido-5-chlorothiophen (70%), previously obtained in 9% yield (Hurd and Moffat, *loc. cit.*) by the action of *N*-chloroacetamide on 2-acetamidothiophen.

The use of 2-phthalimidothiophen offered the possibility of reducing disubstitution. Reaction of 2-aminothiophen with phthalic anhydride in benzene gave *N*-2-thienylphthalamic acid; reaction in xylene gave 2-phthalimidothiophen, also obtained (80%) by dehydration of the phthalamic acid. Use of dimethylformamide as solvent did not improve the yield, and attempted reaction of potassium phthalimide in dimethylformamide solution (Sheehan and Bolhofer, *J. Amer. Chem. Soc.*, 1950, **72**, 2786) with 2-bromo- or 2-iodo-thiophen was unsuccessful.

Reduction of nitrobenzene with iron and acetic acid in presence of phthalic anhydride yielded *N*-phenylphthalimide, and similar treatment of 2-nitrothiophen gave 20% (overall) of 2-phthalimidothiophen. Reduction of 2-nitrothiophen with iron and hydrochloric acid and reaction of the amine hydrochloride with phthaloyl chloride in pyridine gave similar results.

Chlorosulphonation of 2-phthalimidothiophen gave 55% of 5-phthalimidothiophen-2-sulphonyl chloride, smoothly converted into the sulphonamide. By analogy with previous work (Cundiff and Estes, *ibid.*, p. 1424; Steinkopf and Kohler, *Annalen*, 1937, **532**, 264; Cymerman-Craig and Loder, *loc. cit.*) chlorosulphonation is presumed to have occurred in the 5-position; an attempted proof of the 2 : 5-orientation is in progress.

Attempted hydrolysis of 5-phthalimidothiophen-2-sulphonamide by Ing and Manske's method (*J.*, 1926, 2348), by alcoholic sodium ethoxide and hydrazine (cf. Grassmann and Schulte-Uebbing, *Chem. Ber.*, 1950, **83**, 244), by phenylhydrazine in presence of triethylamine (Schumann and Boissonas, *Helv. Chim. Acta*, 1952, **35**, 2235; Scheiber, *Ber.*, 1913, **46**, 1103), or by hydrazine in dimethylformamide or pyridine at 0°, was unsuccessful. Although phthalhydrazide was always formed in good yield, this was accompanied by the evolution of hydrogen sulphide and no basic product could be isolated. 2-Phthalimidothiophen was also immediately cleaved by Ing and Manske's method with evolution of hydrogen sulphide. Acidic or alkaline hydrolysis of 5-phthalimidothiophen-2-sulphonamide proved equally abortive, and either (saturated alcoholic hydrogen chloride or 20% sodium hydroxide) left the compound unchanged or (concentrated hydrochloric acid at 150°) completely ruptured the molecule with formation of phthalic acid, ammonium chloride, and hydrogen sulphide.

The analogous *p*-phthalimidobenzenesulphonamide, prepared by a modification of Wanag and Veinbergs's method (*Ber.*, 1942, **75**, 1558), is reported (Picard, Reid, Reynolds, and Seymour, *J.*, 1948, 821) to give sulphanilamide on acid, and 4-phthalamidobenzenesulphonamide on alkaline hydrolysis. It was unattacked by hydrazine in 5% sodium hydroxide solution or by phenylhydrazine in triethylamine, but was readily cleaved in the expected manner by hydrazine in amyl alcohol at 140° or in dimethylformamide at 20°.

The case with which the 2-phthalimidothiophen compounds undergo ring-opening is clearly due to the nitrogen atom attached to the ring, and may occur after hydrolysis to the amine, which then decomposes through the tautomeric imino-form (an imino-sulphide) (cf. Hurd and Kreuz, *J. Amer. Chem. Soc.*, 1950, **72**, 5543; 1952, **74**, 2965), since 2-phthalimidomethylthiophen derivatives are hydrolysed normally (Cymerman and Faiers, and Cymerman-Craig and Loder, *locc. cit.*).

Further work directed towards the preparation of 5-aminothiophen-2-sulphonamide is in progress.

Experimental

2-Acetamidothiophen.—Methyl 2-thienyl ketoxime (28 g.) in dry ether (300 c.c.) was treated during 15 min. with phosphorus pentachloride (42 g.), the reaction being moderated by occasional cooling (ice). After 30 min., water (50 c.c.) was added dropwise at such a rate that the internal temperature remained below 20°. Sodium hydroxide solution was added with strong

cooling until the pH was 5—6; ether then extracted the crude product. Chromatography in benzene solution on alumina gave 2-acetamidothiophen (15·4 g., 55%) as plates, m. p. 155—156°. One crystallisation from chloroform–benzene raised the m. p. to 160°. Steinkopf (*loc. cit.*) gives m. p. 161—162°.

2-Formylthiophen Diacetate.—2-Formylthiophen (56 g.) was added to acetic anhydride (65 g.), acetic acid (10 c.c.), and anhydrous zinc chloride (1 g.) at <15°. The solid which separated after 8 hr. at room temperature was washed with water and sodium hydrogen carbonate solution, combined with a benzene extract of the neutralised (sodium hydrogen carbonate) mother-liquors, and distilled to give (*a*) 2-formylthiophen (5·5 g.) and (*b*) 2-formylthiophen diacetate (75 g., 78%), b. p. 98—104°/0·3 mm., m. p. 65—67°. Patrick and Emerson (*loc. cit.*) record m. p. 66—68°.

2-Acetamido-5-formylthiophen.—(*a*) Phosphorus oxychloride (14·5 g.) was added dropwise to a stirred solution of 2-acetamidothiophen (10 g.) and *N*-methylformanilide (11·5 g.) in dimethylformamide (25 c.c.) at <10°. The hard yellow cake of aldehyde which was formed after 1 hr. was triturated with benzene, washed with aqueous sodium acetate, and crystallised from ethyl acetate as needles, m. p. 181—182° (8·8 g., 74·5%) (Found : C, 49·75; H, 4·2; N, 8·1; S, 19·1. Calc. for $C_7H_7O_2NS$: C, 49·7; H, 4·2; N, 8·3; S, 19·0%). Campaigne and Archer (*loc. cit.*) give m. p. 183·5—184°. The deep red 2 : 4-*dinitrophenylhydrazone* (from nitrobenzene) had m. p. 307—308° (decomp.) (Found : N, 20·0. $C_{13}H_{11}O_5N_5S$ requires N, 20·0%). The oxime crystallised from water as needles of the *monohydrate*, m. p. 216° (decomp.) (Found : N, 13·95. $C_7H_8O_2N_2S,H_2O$ requires N, 13·85%), becoming anhydrous when at 140° *in vacuo* (Found : C, 46·1; H, 4·4; S, 17·4. Calc. for $C_7H_8O_2N_2S$: C, 45·6, H, 4·4; S, 17·4%); Campaigne and Archer (*loc. cit.*) give m. p. 198—202°. The *semicarbazone* (from aqueous alcohol) had m. p. 260·5—261° (Found : C, 40·7; H, 4·75. $C_8H_{10}O_2N_4S,\frac{1}{2}H_2O$ requires C, 40·85; H, 4·7%), and the thiosemicarbazone (from methanol) had m. p. 237° (Found : C, 39·9; H, 4·65; N, 21·65. Calc. for $C_8H_{10}ON_4S_2,\frac{1}{2}CH_3{\cdot}OH$: C, 39·55; H, 4·7; N, 21·7%); Campaigne, Monroe, Arnwine, and Archer (*loc. cit.*) give m. p. 231—233°.

(*b*) A solution of 2-formyl-5-nitrothiophen diacetate (12·6 g.; Patrick and Emerson, *loc. cit.*) in acetic acid (50 c.c.) containing acetic anhydride (7·5 g.) was reduced at 50—60° by gradual addition of powdered iron (16·4 g.), additional quantities of acetic acid (30 c.c.) and acetic anhydride (2 c.c.) being added when all the iron had been introduced. After 2 hr. at 50—60°, neutralisation of the cooled mixture with sodium hydrogen carbonate precipitated a solid, isolated by extraction into hot ethanol. The product obtained by removal of this solvent was taken up in hot water, and, after brief acid hydrolysis (dilute hydrochloric acid), yielded the 2 : 4-dinitrophenylhydrazone, semicarbazone, and thiosemicarbazone of 2-acetamido-5-formylthiophen identical (m. p. and mixed m. p.) with the derivatives prepared as in (*a*). The yield, based on that of the 2 : 4-dinitrophenylhydrazone, was 32%.

N-2-Thienylphthalamic Acid.—2-Thienylammonium chlorostannate (10·8 g.; Steinkopf, *loc. cit.*; Hartough, "Thiophene and its Derivatives," Interscience, New York, 1952) was shaken under nitrogen with sodium hydroxide solution (50 c.c.; 40% w/v) at 40° for 30 sec. The liberated 2-aminothiophen was extracted with benzene (5 × 50 c.c.), the phases were separated by centrifugation at 3000 r.p.m. for 1 min., and the benzene layer (washed with saturated sodium chloride under nitrogen) was immediately run into a suspension of finely powdered phthalic anhydride (6 g.) in benzene (10 c.c.), which was sealed under nitrogen for 45 min. Slow evaporation (30 min.) of the solution left a residue which on extraction with sodium hydrogen carbonate solution and acidification of the extract to pH 1 gave N-2-*thienylphthalamic acid* (0·5—2·0 g., 5—20%) (Found : C, 58·2; H, 3·9. $C_{12}H_9O_3NS$ requires C, 58·3; H, 3·7%). The compound had no true m. p., but cyclised at 160—170° and then had the m. p. of 2-phthalimidothiophen.

2-Phthalimidothiophen.—(*a*) *N*-2-Thienylphthalamic acid (0·6 g.) was heated at 170° for 45 min. *in vacuo* (10 mm.) over phosphoric oxide. Crystallisation from ethanol afforded yellow needles of *2-phthalimidothiophen* (0·45 g., 80%), m. p. 198° (Found : C, 62·6; H, 3·3. $C_{12}H_7O_2NS$ requires C, 62·8; H, 3·1%).

(*b*) 2-Phthalimidothiophen (1 g., 11%) was the sole product obtained when xylene replaced benzene in the preparation of *N*-2-thienylphthalamic acid described above.

(*c*) A solution of 2-nitrothiophen (60 g.) and phthalic anhydride (76 g.) in acetic acid (300 c.c.) and water (80 c.c.) was treated with iron powder (100 g.) during 2 hr., the temperature being kept at 50—60°. After a further 2·5 hr. the cooled mixture was poured into ice-water (1500 c.c.) and brought to pH 3 by addition of hydrochloric acid. The product which separated was chromatographed in benzene solution on alumina, giving 2-phthalimidothiophen (21·6 g., 20%

overall from 2-nitrothiophen), m. p. 198°, identical with material obtained by methods (*a*) and (*b*).

(*d*) A suspension of 2-nitrothiophen (2·58 g.) in 10N-hydrochloric acid (50 c.c.) at 50° was treated with iron powder (6 g.). Reduction was complete in 30 min.; then the cooled and filtered solution was treated at 0° with phthaloyl chloride (4·1 g.) and excess of pyridine. The red colour was discharged in 15 min. and replaced by a precipitate of 2-phthalimidothiophen (0·9 g., 20%), isolated by dilution with water, extraction with benzene, and chromatography on alumina.

5-Phthalimidothiophen-2-sulphonyl Chloride.—2-Phthalimidothiophen (2·29 g.) was added during 25 min. to redistilled chlorosulphonic acid (9·4 g.) at −5°, and the mixture kept at this temperature for a further 30 min. External cooling was removed and, after a further 45 min. at 25°, dry chloroform (10 c.c.) was added and the whole poured into ice (100 g.), from which the product was extracted with chloroform. Removal of solvent from the washed (water) and dried (Na_2SO_4) extracts gave *5-phthalimidothiophen-2-sulphonyl chloride* (1·8 g., 55%), crystallising from chloroform–light petroleum (b. p. 60—90°) in pale yellowish plates, m. p. 176·5° (decomp.) (Found: C, 43·7; H, 2·1. $C_{12}H_6O_4NS_2Cl$ requires C, 44·0; H, 1·9%).

5-Phthalimidothiophen-2-sulphonamide.—The foregoing sulphonyl chloride (0·7 g.) in chloroform (30 c.c.) was treated with dry ammonia. Separation of the sulphonamide commenced almost immediately and was complete in 45 min. The residual *amide* obtained on removal of solvent was triturated with water, and crystallised from nitrobenzene or pyridine as yellow plates, m. p. 261° (decomp.) (0·52 g., 79%) (Found: N, 9·1. $C_{12}H_8O_4N_2S_2$ requires N, 9·1%).

The same product was obtained in 51% overall yield from 2-phthalimidothiophen when isolation of the pure sulphonyl chloride was omitted.

2-Acetamido-5-chlorothiophen.—Treatment of 2-acetamidothiophen (2 g.) in tetrachloroethane (120 c.c.) at 5° with sulphuryl chloride (2·4 g.) in tetrachloroethane (20 c.c.) gave crystals after 15 min. The reaction was completed by 2 hours' stirring at room temperature. The residue obtained on removal of the solvent *in vacuo* crystallised from chloroform–light petroleum (b. p. 60—90°) and, after chromatography on alumina in benzene, gave needles, m. p. 179°, of 2-acetamido-5-chlorothiophen (1·75 g., 70%) (Found: C, 41·5; H, 3·4; N, 7·7; O, 9·2; S, 18·4. Calc. for C_6H_6ONSCl: C, 41·0; H, 3·4; N, 8·0; O, 9·1; S, 18·3%). Hurd and Moffat (*loc. cit.*) give m. p. 177·5—178°.

4-Phthalimidobenzenesulphonamide.—Sulphanilamide (17·2 g.) and phthalic anhydride (25 g.) were heated under reflux for 5 hr. in acetic acid (250 c.c.). Evaporation *in vacuo* and dilution with water gave 4-*o*-carboxybenzoylaminobenzenesulphonamide in almost quantitative yield, readily cyclised by boiling with nitrobenzene (200 c.c.) for 3 hr. 4-Phthalimidobenzenesulphonamide separated as a white micro-crystalline solid, m. p. 322—323° (28·6 g., 95% overall yield). Wanag and Veinbergs (*loc. cit.*) give m. p. 320—322°.

Hydrolysis. The foregoing sulphonamide (3·02 g.) in amyl alcohol (20 c.c.) was heated with 100% hydrazine hydrate (1·03 g., 2 mols.) under reflux for 2·5 hr. The intermediate was decomposed with alcoholic hydrogen chloride to yield phthalhydrazide (1·3 g., 80%). The solution was shown to contain sulphanilamide and was not further investigated.

N-Phenylphthalimide.—Nitrobenzene (10 g.) and phthalic anhydride (12·5 g.) in aqueous acetic acid (60 c.c., 75%) at 60° were treated with iron powder (20 g.), the temperature being 60—70° throughout. After 2 hr., dilution of the cooled mixture to 500 c.c., extraction of the precipitated solid with chloroform, and evaporation gave *N*-phenylphthalimide (2·1 g., 12%) as needles, m. p. 204—205° undepressed on admixture with an authentic specimen.

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The Photolysis of Acetaldehyde. Part III. The Reaction in the Presence of Nitric Oxide.*

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The photolysis of acetaldehyde at high temperatures (250—300°) in the presence of nitric oxide has been studied, chiefly by mass-spectrometric analysis of the products of the reaction. The rates of consumption of aldehyde and nitric oxide are approximately equal. Ethane is not a product of the inhibited reaction. Reactions of nitric oxide with the CHO radical (or with hydrogen atoms derived from it) either do not take place to any considerable extent or are followed by substantially complete regeneration of the nitric oxide. The fate of the nitric oxide is discussed. Estimates are made of the relative contributions of radical production and molecular rearrangement to the primary process at 2537 and 3130 Å.

The photolysis of acetaldehyde at temperatures in the region 250—300° is strongly inhibited by small amounts of nitric oxide. Mitchell and Hinshelwood (*Proc. Roy. Soc.*, 1937, **159**, 32) found that a few units % of nitric oxide reduced the quantum efficiency from large values to unity. Estimates of the overall collision efficiency for the reaction of nitric oxide with alkyl radicals have been made (Forsyth, *Trans. Faraday Soc.*, 1941, **37**, 312; Durham and Steacie, *J. Chem. Phys.*, 1952, **20**, 582) but the precise mechanism by which nitric oxide inhibits low-temperature reactions, and in particular the final fate of the nitric oxide itself, are by no means clear. An analytical study of the products of the photolysis of acetaldehyde in the presence of nitric oxide has therefore been made in the hope of throwing some light on this problem. The photolysis of acetaldehyde itself has been the subject of a number of recent studies and the main features of the reaction are well established. A number of obscurities remain. In particular, little is known of the part played by the CHO radicals or of the mechanism by which hydrogen is formed. Information on these points may also be obtained from a study of the photolysis in the presence of nitric oxide. Values for the relative contributions of radical production and of direct molecular rearrangement to the primary process may be derived from a knowledge of the rates of methane formation in the normal and the fully inhibited reaction.

Experimental

The experimental methods were essentially similar to those previously employed (Danby, Buchanan, and Henderson, *J.*, 1951, 1426). Two sources of radiation were used, a Thermal Syndicate low-pressure mercury lamp radiating almost entirely at 2537 Å, and a 125-w Osira mercury lamp with the outer glass envelope removed, operated in conjunction with filters to isolate the region around 3130 Å (Bowen, *J.*, 1935, 76). Both lamps were supplied from a constant-voltage transformer.

Analyses of reaction products were made with a Metropolitan-Vickers mass-spectrometer Type M.S.2, conventional techniques being used. In a number of experiments the amounts of unchanged aldehyde and nitric oxide were also determined by chemical analysis, the method of Danby and Hinshelwood (*Proc. Roy. Soc.*, 1941, *A*, **179**, 169) being used for the former, and that of Musgrave and Hinshelwood (*ibid.*, 1932, *A*, **132**, 23) for the latter. The mass-spectrometer gave results in excellent agreement with those obtained by chemical methods.

Results and Discussion

The Relative Reaction Rates of Aldehyde and Nitric Oxide.—Table 1 gives the results of analyses of the products of the photolysis of acetaldehyde in the presence of nitric oxide by radiation of wave-length 3130 Å. Similar experiments were carried out at 2537 Å. The results are summarised in Table 2, together with data for the uninhibited reaction.

The ratio of the rate of formation of methane to that of carbon monoxide, which is

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TABLE 1. *Products of photolysis of acetaldehyde in presence of nitric oxide at* 3130 Å *and* 300°.

(Initial pressures: CH_3·CHO 100 mm., NO 50 mm.)

CH_3·CHO decomposed, mm.	NO reacted, mm.	CO formed, mm.	CH_4 formed, mm.	H_2 formed, mm.	CH_3·CHO decomposed, mm.	NO reacted, mm.	CO formed, mm.	CH_4 formed, mm.	H_2 formed, mm.
3·3	3·5	3·5	0·25	0·06	4·6	4·5	4·5	0·29	0·10
4·2	4·4	4·3	0·35	0·10	6·0	6·3	6·4	0·50	0·15

TABLE 2.

NO/ CH_3·CHO	CO/ CH_3·CHO	CH_4/CO	H_2/CO	C_2H_6/CO	NO/ CH_3·CHO	CO/ CH_3·CHO	CH_4/CO	H_2/CO	C_2H_6/CO
3130 Å, inhibited					3130 Å, uninhibited				
1·06	1·06	0·07	0·02	0	—	0·82	0·95	0·01	0·04
1·04	1·02	0·08	0·02	0	—	0·93	0·92	0·02	0·04
0·98	0·98	0·06	0·02	0	—	0·95	0·93	0·02	0·03
1·05	1·07	0·08	0·02	0	—	0·97	0·90	0·02	0·04
					—	0·96	0·90	0·02	0·04
2537 Å, inhibited									
1·04	0·93	0·18	0·08	0					
0·99	1·07	0·19	0·08	0					
1·01	1·07	0·16	0·08	0					

(The values for aldehyde and nitric oxide represent the amounts which have *reacted*: those for products are amounts *formed*.)

practically unity for the uninhibited reaction, is reduced in the presence of nitric oxide to a small value, but not to zero. No ethane could be detected in the products of the inhibited reaction. The detection of small amounts of ethane by mass-spectrometer in gas mixtures containing nitric oxide presents special problems which have been discussed by Danby, Spall, Stubbs, and Hinshelwood (*Proc. Roy. Soc.*, 1954, *A*, **223**, 421). In a series of experiments, samples of the products of the photolysis of aldehyde in the presence of nitric oxide were treated with moist sodium hydrogen sulphite or sodium hydroxide to remove unchanged aldehyde and with moist ferrous sulphate to remove nitric oxide before admission to the mass-spectrometer. Under these conditions very small traces of ethane, if present, would have been detected. These experiments proved negative.

The following reaction mechanism adequately accounts for the main features of the acetaldehyde photolysis at elevated temperatures (Leermakers, *J. Amer. Chem. Soc.*, 1934, **56**, 1537):

$$CH_3\cdot CHO + h\nu = CH_4 + CO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$CH_3\cdot CHO + h\nu = CH_3 + CHO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$CH_3 + CH_3\cdot CHO = CH_4 + CO + CH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$2CH_3 = C_2H_6 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Estimates of the relative participation of reactions (1) and (2) in the primary process have been made by Gorin (*Acta Physiochim. U.R.S.S.*, 1938, **9**, 691; *J. Chem. Phys.*, 1938, **7**, 257) and by Blacet and Heldman (*J. Amer. Chem. Soc.*, 1942, **64**, 889, 893) from studies of the photolysis in the presence of iodine vapour. Further evidence on this point from the present work will be discussed later. Reaction (2) largely predominates, especially at longer wave-lengths. If we therefore neglect reaction (1) for the moment it follows from the equality in the rates of consumption of aldehyde and nitric oxide that either the methyl or the formyl radical from reaction (2), but not both, can react with nitric oxide to produce a stable complex. As the formation of ethane is completely suppressed by nitric oxide while that of carbon monoxide is unaffected, it is clearly the methyl radical which reacts. In the presence of nitric oxide, therefore, the reaction

$$CH_3 + NO = \text{products} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

completely replaces reactions (3) and (4). If the formyl radicals interact with nitric oxide a cycle of reactions must ensue which leads to substantially complete regeneration of the nitric oxide and carbon monoxide, such as

$$CHO + NO = CHO\cdot NO \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$2CHO\cdot NO = 2CO + 2NO + H_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Alternatively, if the formyl radical dissociates on formation, similar considerations must apply to the hydrogen atom formed:

$$CHO = CO + H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$
$$H + NO = NOH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$
$$2NOH = 2NO + H_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

The Fate of the Nitric Oxide.—Although an amount of nitric oxide roughly equal to that of the aldehyde decomposed undergoes reaction, only small amounts of nitrogen-containing compounds can be detected in the gaseous reaction products. The immediate addition product of a methyl radical and nitric oxide would be $CH_3 \cdot NO$ and Raley, Rust, and Vaughan (*J. Amer. Chem. Soc.*, 1948, **70**, 88) have reported the detection of appreciable amounts of the isomer formaldoxime, $CH_2{:}N \cdot OH$, in the products of the thermal decomposition of di-*tert.*-butyl peroxide in the presence of nitric oxide at about 210°. Small peaks at *M*/*e* 45 are present in the mass-spectra of some of the samples of products of the aldehyde photolysis in presence of nitric oxide but they correspond to amounts of formaldoxime far too small to account for more than a fraction of the nitric oxide consumed. At much higher temperatures (630°) a large proportion of the nitric oxide interacting with alkyl radicals appears in the final products in the form of hydrogen cyanide (Danby, Spall, Stubbs, and Hinshelwood, *Proc. Roy. Soc.*, 1953, *A*, **218**, 430). No trace of hydrogen cyanide or ammonia could be detected by mass spectrometer or chemical tests in the products of the inhibited aldehyde photolysis at 300°. Formaldoxime is known to polymerise very readily to a solid trimer (Schall, *Ber.*, 1891, **24**, 573). The evidence therefore suggests that the interaction of methyl radicals with nitric oxide leads to the formation of formaldoxime which, at 300°, polymerises to a solid of low vapour pressure, and at higher temperatures decomposes to form hydrogen cyanide and water.

The Formation of Hydrogen.—In the uninhibited reaction the amount of hydrogen in the products is small, being almost exactly half that of the ethane (Table 2). It can be shown that this is the ratio of ethane to hydrogen which would be obtained were the hydrogen entirely formed by the reaction

$$CHO + CH_3 \cdot CHO = H_2 + 2CO + CH_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

Both the alternative fates for the formyl radical in the presence of nitric oxide given by (6) and (7) or by (8), (9), and (10) would lead to the formation of an amount of hydrogen in the inhibited reaction equal to half that of the carbon monoxide. The analytical results show that only a small proportion of this amount of hydrogen is actually present in the products. The close equivalence of the amounts of aldehyde decomposed and of carbon monoxide formed rules out reactions such as the formation of glyoxal. In the same way the figures for the rate of consumption of nitric oxide show that reactions such as

$$2NOH = H_2O + N_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

cannot be taking place to a very great extent. Small amounts of water vapour, nitrogen, and nitrous oxide are, in fact, present in the reaction products but the amounts are too small to account for the large discrepancy in the amounts of hydrogen. It has, however, been observed recently that olefins such as propylene and butene are as powerful inhibitors of the exchange reaction between hydrogen and deuterium as is nitric oxide (unpublished observations, this laboratory). As formaldoxime contains a double bond, it seems probable that it may react with hydrogen atoms in a similar manner. The product of such an interaction would be a free radical which might therefore polymerise the more readily, thus providing a further reason for the absence of appreciable amounts of formaldoxime in the volatile products.

The Effect of Wave-length on the Primary Process.—The rate of reaction (1) is given by the rate of formation of methane in the inhibited reaction; that of reaction (2) by subtraction of the rate of (1) from the rate of consumption of aldehyde. We thus obtain the values for the relative probabilities of molecular rearrangement and radical formation in

the primary process given in Table 3. The values obtained fall between those of Gorin and of Blacet and Heldman (*locc. cit.*) at the longer wave-length but correspond to a lower relative probability of molecular rearrangement at 2537 Å than either of those previously reported. The earlier work, however, relates to photolysis at much lower temperatures.

The results in Table 3 show that approximately 9% and 17% of the aldehyde decomposes without forming radicals at 3130 and 2537 Å, respectively. As the consumption of nitric

TABLE 3. *Contributions of molecular rearrangement and radical formation to the aldehyde primary process at 300°.*

Wave-length	$CH_4/(CO - CH_4)$			Wave-length	$CH_4/(CO - CH_4)$		
3130 Å	0·07 0·09 0·07 0·09	Mean 0·08	Molecular 9·3% Radical 90·7%	2537 Å	0·22 0·23 0·19	Mean 0·21	Molecular 17·3% Radical 82·7%

oxide is nearly equal to that of aldehyde at both wave-lengths it follows that a small amount of nitric oxide reacts in some way other than with methyl radicals. The equivalence of the amounts of aldehyde decomposed and of carbon monoxide formed shows that a stable complex of nitric oxide and the formyl radical is not formed. The presence of small amounts of nitrous oxide and of water vapour in the products as already mentioned suggests that reactions such as (12) probably take place to a sufficient extent to account for the difference.

We thank Professor Sir Cyril Hinshelwood for his help and interest throughout this work.

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A Modified Benziminazole Synthesis. Part II. A Route to Unsymmetrically Substituted 2 : 2′-Dibenziminazolyls and Methylenebis-2-benziminazoles.*

By E. S. LANE.

[Reprint Order No. 5934.]

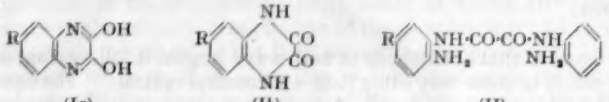
The mechanism of the formation of 2 : 2′-dibenziminazolyls and methylenebis-2-benziminazoles from *o*-diamines and oxamide and malonamide respectively is discussed, and the preparation of some unsymmetrically substituted compounds, which support the proposed mechanism, described.

WHEREAS oxalic acid or its esters react with *o*-phenylenediamine to form 2 : 3-dihydroxyquinoxaline (I*a*; R = H), yet it was shown in Part I * that the use of oxamide in this reaction gave 2 : 2′-dibenziminazolyl (III; R = H) as the chief product. Further experimental work has now indicated that 2 : 3-dihydroxyquinoxaline is, in fact, formed first and that this reacts with another molecule of diamine to form (III; R = H). Thus, with one equivalent of *o*-phenylenediamine dihydrochloride, oxamide reacted to form (I*a*; R = H), and with two equivalents (III; R = H) was formed (see Part I). Preformed (I*a*; R = H) similarly reacted with *o*-phenylenediamine dihydrochloride, giving (III; R = H). Further evidence was obtained from reaction of oxamic acid with first one, and then two, equivalents of *o*-phenylenediamine, the main products being respectively (I*a*; R = H) and (III; R = H). The conversion of a quinoxaline ring system into that of a benziminazole ring has not hitherto been noted but it seems likely that this reaction is another example of Galat and Elion's method of acylation (*J. Amer. Chem. Soc.*, 1943, **65**, 1566). Thus, if (I*a*; R = H) is regarded as reacting in its diketo-form (I*b*; R = H) with *o*-phenylenediamine, it can undergo a form of " ammonolysis " with the formation of

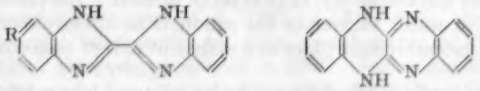
* The communication " A Modified Benziminazole Synthesis," *J.*, 1953, 2238, is regarded as Part I.

the highly labile compound (II; R = H) which is spontaneously dehydrated and cyclised to form (III; R = H). The latter step is, of course, a well-known feature of the formation of 2-substituted benziminazoles by reduction of acylated *o*-nitroanilines.

This reaction sequence has been used for the preparation of an unsymmetrically substituted 2 : 2′-dibenziminazolyl, since 2 : 3-dihydroxy-6-methylquinoxaline (I*a*; R = Me) and *o*-phenylenediamine dihydrochloride reacted to form 5-methyl-2 : 2′-dibenziminazolyl (III; R = Me). The identity of the product was confirmed by comparison of the *X*-ray powder photograph of its diacetate with those of samples prepared by two alternate routes from 2-trifluoromethyl-substituted benziminazoles (Lane, *J.*, 1955, 534). The main product from the new reaction is heavily contaminated with highly-coloured products of type (IV) (see Hinsberg, *Ber.*, 1896, **29**, 784). Acid solutions of these types of compound are brilliantly fluorescent in ultra-violet light, but the fluorescent colour (yellow-green) is



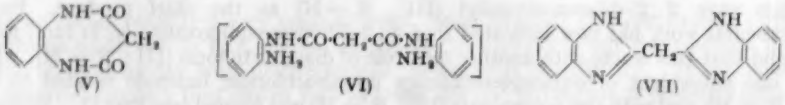
(I*a*) (I*b*) (II)



(III) (IV)

quite different from that of the dibenziminazolyls (blue) and this enables one type of compound to be detected in the presence of the other. Although another route to unsymmetrically substituted benziminazoles is now provided, this contamination by difficultly removable by-products renders it of little synthetic use in comparison with the route *via* 2-trifluoromethyl-substituted benziminazoles. Furthermore, there are limitations to the scope of the reaction; *e.g.*, 2 : 3-dihydroxyquinoxaline failed to react with the salts of either 3 : 4-diaminotoluene or 4-nitro-*o*-phenylenediamine.

In an analogous way, the formation of methylenebis-2-benziminazoles from *o*-diamines and malonamide (cf. Part I) is believed to involve *o*-phenylenemalonamide (V) as an intermediate product. By reaction of (V) with a further molecule of *o*-phenylenediamine dihydrochloride, methylenebis-2-benziminazole (VII) has been obtained, presumably *via* the intermediate compound (VI). This interesting conversion of a 7- into a 5-membered ring system is of greater synthetic value than the previous example since there are no coloured by-products, and the reaction has been extended to include the preparation of the unsymmetrical compound 4 : 7-diethoxymethylenebis-2-benziminazolyl from *o*-phenylenemalonamide and 2 : 3-diaminoquinol diethyl ether hydrochloride.



(V) (VI) (VII)

It is noteworthy that whereas both the 2 : 2′-dibenziminazolyls and the methylenebis-2-benziminazoles formed diacetates and/or dihydrochlorides, the former group of compounds behaved only as monofunctional bases towards perchloric acid in glacial acetic acid. Although some functions are not always fully developed during titrations in glacial acetic acid, it is probable that this is a further example of steric interference with salt formation. Similar behaviour has been noted in the cases of *o*-phenanthroline, 2 : 2′-dipyridyl, and certain analogues of 2 : 2′-dipyridyl containing *iso*quinoline and thiazole rings (Knott and Breckenridge, *Canad. J. Chem.*, 1954, **32**, 512) which form only monopicrates. Like 2 : 2′-dibenziminazolyl, *o*-phenanthroline and 2 : 2′-dipyridyl behave only as monoacid bases towards perchloric acid in glacial acetic acid.

Experimental

The equivalent weights of the benziminazoles were determined by titration with 0·1N-perchloric acid in glacial acetic acid, crystal-violet being used as indicator (Fritz, "Acid-Base Titrations in Nonaqueous Solvents," G. F. Smith Chemical Co., Columbus, 1952).

2 : 2′-*Dibenziminazolyl*.—**2 : 3**-Dihydroxyquinoxaline (3·24 g.), *o*-phenylenediamine (2·16 g.), and ethylene glycol were refluxed for 8 hr., during which crystalline material slowly separated. The mixture was poured into water, and the yellow solid filtered off. The above base, crystallised from ethylene glycol (carbon), formed yellow needles which did not melt below 400° (Found: C, 72·1; H, 4·7; N, 23·6%; equiv., 232. Calc. for $C_{14}H_{10}N_4$: C, 71·8; H, 4·3; N, 23·95%; equiv., 234). The *diacetate* (pale yellow needles from glacial acetic acid) had no definite m. p. (Found: C, 60·6; H, 4·7; N, 15·3. $C_{18}H_{14}O_4N_4$ requires C, 61·0; H, 5·1; N, 15·8%).

Reaction of Oxamic Acid with o-*Phenylenediamine*.—Equimolecular quantities (0·05 mole) of this acid and base when refluxed in ethylene glycol for 5 hr. gave a 64% yield of **2 : 3**-dihydroxyquinoxaline (fine cream needles from ethylene glycol), m. p. 386° (Found: C, 59·1; H, 3·6; N, 17·4. Calc. for $C_8H_6O_2N_2$: C, 59·2; H, 3·7; N, 17·3%. Repetition of this experiment with twice the quantity of *o*-phenylenediamine gave **2 : 2′**-dibenziminazolyl (51%) as bright yellow needles (ethylene glycol) (Found: N, 24·0%; equiv., 235).

5-Methyl-**2 : 2′-*dibenziminazolyl*—2 : 3**-Dihydroxy-6-methylquinoxaline (2 g.), *o*-phenylenediamine dihydrochloride (2 g.), and ethylene glycol (15 ml.) similarly gave the above base (2·3 g.) as yellow crystals (aqueous ethanol), melting indistinctly at 380—390° (decomp.). The *diacetate* (Found: C, 62·0; H, 5·3; N, 15·2. $C_{19}H_{20}O_4N_4$ requires C, 61·9; H, 5·4; N, 15·2%), the *sulphate* (Found: C, 39·8; H, 3·75; N, 12·9. $C_{15}H_{12}N_4,2H_2SO_4$ requires C, 40·5; H, 3·6; N, 12·6%), and the *monopicrate* (Found: N, 20·9. $C_{21}H_{15}O_7N_7$ requires N, 20·55%) had indefinite m. p.s (cf. Lane, *loc. cit.*).

Methylenebis-**2**-*benziminazole*.—*o*-Phenylenemalonamide (1·76 g.), *o*-phenylenediamine dihydrochloride (2·0 g.), and ethylene glycol were refluxed for 4 hr. The mixture was poured into water, neutralised with ammonia, and filtered. The base melted at 380—390° (decomp.) (see Part I) (Found: C, 72·0; H, 4·8; N, 22·3%; equiv., 124. Calc. for $C_{15}H_{12}N_4$: C, 72·5; H, 4·8; N, 22·6%; equiv., 124). The *dipicrate* melted at 246—247° (alcohol, dimethylformamide) (Found: N, 20·2%; equiv., 354. $C_{27}H_{18}O_{14}N_{10}$ requires N, 19·7%; equiv., 353). The equivalent was determined by Clark and Wang's method (*Analyt. Chem.*, 1954, **26**, 1230).

4 : 7-*Diethoxymethylenebis*-**2**-*benziminazolyl*.—**2 : 3**-Diaminoquinol diethyl ether hydrochloride (Lane and Williams, *J.*, 1953, 4187) (2·3 g.), *o*-phenylenemalonamide (1·76 g.), and ethylene glycol (15 ml.) were refluxed for 2 hr., and worked up as before. The above *base* (2·9 g.) formed a straw-yellow powder (ethylene glycol; carbon) shrinking with decomposition at 270° with no definite m. p. (Found: C, 68·2; H, 6·1; N, 16·6%; equiv., 165. $C_{19}H_{20}O_2N_4$ requires C, 67·8; H, 5·95; N, 16·65%; equiv., 168). The *dihydrochloride* (cream prisms) decomposed, when slowly heated to 270°, without melting (Found: N, 14·2; Cl, 17·6. $C_{19}H_{20}O_2N_4,2HCl$ requires N, 13·7; Cl, 17·4%).

The author is indebted to Dr. J. Adam (A.E.R.E.) for a number of *X*-ray powder photographs.

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Carcinogenic Nitrogen Compounds. Part XVII. The Synthesis of Angular Benzacridines.*

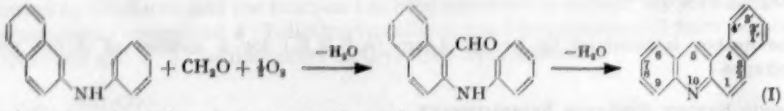
By Ng. Ph. Buu-Hoï, René Royer, and Michel Hubert-Habart.

[Reprint Order No. 5940.]

Some features of the synthesis of benzacridines by the Ullmann–Fetvadjian and the Bernthsen method have been more closely investigated, and the reaction between paraformaldehyde, *m*-toluidine, and 1- or 2-naphthol is shown to give two isomeric angular methylbenzacridines in each case. The Mayer cyclisation of diarylamine-*o*-aldehydes has been successfully extended to the synthesis of 3 : 4-benzacridine and related compounds, and a number of new homologues of 1 : 2- and 3 : 4-benzacridine have been prepared for testing as potential carcinogens.

In the Ullmann–Fetvadjian reactions between *m*-toluidine, paraformaldehyde, and 1- or 2-naphthol, the cyclisation can theoretically involve the positions *ortho* or *para* to the methyl group, which would give 6- and 8-methyl-1 : 2- or 6- and 8-methyl-3 : 4-benzacridine, respectively. The formation of two isomers would be parallel to the behaviour of *m*-substituted anilines in the various quinoline cyclisations. Hitherto, only 8-methyl-1 : 2- and -3 : 4-benzacridine had been obtained in this way, the 6-methyl isomers being prepared by pyrolysis of *N*-2′ : 3′-xylyl-1- and -2-naphthylamine with lead oxide (Buu-Hoï, *J.*, 1949, 670). The isolation of small quantities of 6-methyl-1 : 2- and -3 : 4-benzacridine in the Ullmann–Fetvadjian reaction has now been achieved by fractional crystallisation of the picrates of the crude bases obtained. The *ortho*-cyclisation was not observed in the reaction of *m*-toluidine and 6-methyl-2-naphthol with paraformaldehyde, only 8 : 2′-dimethyl-3 : 4-benzacridine (Buu-Hoï, Royer, Hubert-Habart, and Mabille, *J.*, 1953, 3584) being obtained. Nor did the Bernthsen reaction between *N*-*m*-tolyl-2-naphthylamine, acetic anhydride, and zinc chloride yield two isomers, 5 : 8-dimethyl-3 : 4-benzacridine (Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792) alone being isolated.

The mechanism of the Ullmann–Fetvadjian condensation is still unknown, but there is some evidence that it involves the intermediate formation of diarylamines rather than diarylmethanes (cf. Albert, "The Acridines," Arnold, London, 1951, p. 90); such being the case, a possibility would be a transient conversion of the diarylamine into an *ortho*-aldehyde which would subsequently undergo thermal cyclodehydration, as in the Mayer acridine synthesis (Kalischer and Mayer, *Ber.*, 1916, **49**, 1994; Mayer and Stein, *Ber.*, 1917, **50**, 1306). In the reaction of 2-naphthol with aniline and paraformaldehyde, for instance, the mechanism would be :

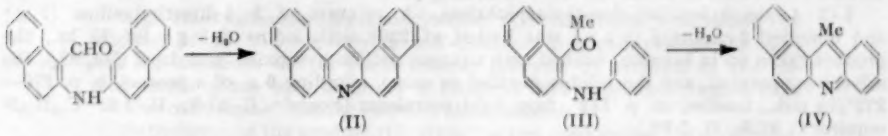


It has now been found that 2-anilino-1-formylnaphthalene undergoes cyclisation to 3 : 4-benzacridine on pyrolysis or, better, when heated with sulphuric acid in acetic acid (cf. Albert, *J.*, 1948, 1225). 3 : 4-6 : 7-Dibenzacridine (II) was similarly prepared from 1-formyldi-2-naphthylamine. These two aldehydes were obtained by treating *N*-phenyl-2-naphthylamine and di-2-naphthylamine, respectively, with *N*-methylformanilide and phosphorus oxychloride.

The mechanism of the Bernthsen synthesis of 5-substituted acridines has been postulated as involving the intermediate formation of *ortho*-amino-ketones (Albert, *op. cit.*, p. 67), a hypothesis which would account well for the high yields observed in the syntheses of 5-substituted angular benzacridines. In the reaction between *N*-phenyl-2-naphthylamine and acetic acid in the presence of zinc chloride, 1-acetyl-2-anilinonaphthalene (III) would be the intermediate; this ketone was prepared by a Knoevenagel reaction (*J.*

* Part XVI, Buu-Hoï and Jacquignon, *J.*, 1954, 513.

pr. Chem., 1914, **89**, 1; Buu-Hoï, *J.*, 1952, 4346) of aniline with 1-acetyl-2-naphthol, and found to cyclise readily to (IV). Further support for the intermediate formation of amino-ketones is the fact that, although such ketones had not been isolated as a result of normal Bernthsen reactions, they could be obtained in the reaction of organic acids and zinc chloride on certain diarylamines such as carbazole which are unable to undergo acridine cyclisations. Bizzari (*Gazzetta*, 1890, **20**, 407, 414; 1891, **21**, 159, 352; 1892,



(II) (III) (IV)

23, 1) claimed to have obtained " carbazoacridines " in the reaction of carbazole with acetic and benzoic acid under these conditions, but it has recently been suggested (Acheson and Sansom, *J.*, 1953, 1900) that these " carbazoacridines " are impure 3-acetyl- and 3-benzoyl-carbazole, and this is now confirmed.

For biological testing as potential carcinogens, a number of new homologues of 1 : 2- and 3 : 4-benzacridine bearing one or more substituents (some with long alkyl chains) were prepared by the Ullmann–Fetvadjian and the Bernthsen method; they are listed in the Table.

Experimental (with B. Eckert)

Reaction of m-*Toluidine and* 2-*Naphthol.*—To a boiling mixture of purified *m*-toluidine (15 g.) and 2-naphthol (21 g.), paraformaldehyde (4·5 g.) was added in small portions. When evolution of water ceased, the product was refluxed for 1 min. and fractionated, giving an orange-yellow resin, b. p. 265—275°/30 mm., which was dissolved in ethanol and treated with picric acid. The crude picrate (15 g.) gave on recrystallisation from nitrobenzene two fractions: (*a*) 8-methyl-3 : 4-benzacridine picrate, orange-yellow prisms, m. p. 263—264°, which on treatment with aqueous ammonia yielded the free base (5 g.), almost colourless needles, m. p. 144°, from methanol (Buu-Hoï, *J.*, 1949, **670**, gave m. p. 143° for 8-methyl-3 : 4-benzacridine and m. p. 262—263° for its picrate); (*b*) 6-methyl-3 : 4-benzacridine pictrate, m. p 278°, whose base (0·8 g.) crystallised as almost colourless needles, m. p. 130°, from methanol (Buu-Hoï, *loc. cit.*, gave m. p. 129° for 6-methyl-3 : 4-benzacridine and m. p. 276—278° for the picrate).

Preparation of 6- *and* 8-*Methyl*-1 : 2-*benzacridine.*—A similar reaction performed on *m*-toluidine (20 g.), α-naphthol (28 g.), and paraformaldehyde (6 g.) afforded an oily benzacridine mixture, b. p. 260—270°/15 mm. Fractional crystallisation of the picrates from nitrobenzene gave: (*a*) 8-methyl-1 : 2-benzacridine picrate, orange-yellow needles, m. p. 241—242°, whose base formed pale yellow prisms (2 g.), m. p. 148°, from methanol (Buu-Hoï, *loc. cit.*, gave m. p. 148° for the base and m. p. 239—240° for the picrate); (*b*) 6-methyl-1 : 2-benzacridine picrate, orange-yellow needles, m. p. 251°, whose base formed yellowish prisms (0·5 g.), m. p. 136°, from methanol (Buu-Hoï, *loc. cit.*, gave m. p. 136° for 6-methyl-1 : 2-benzacridine, and m. p. 249—251° for the picrate).

A search for similar pairs of isomers in the Ullmann–Fetvadjian reaction of 6-methyl-2-naphthol with *m*-toluidine and paraformaldehyde, and in the Bernthsen condensation of *N*-*m*-tolyl-2-naphthylamine with acetic anhydride, was unsuccessful.

Synthesis of Benzacridines by the Mayer Reaction.—A mixture of *N*-phenyl-2-naphthylamine (3 g.), *N*-methylformanilide (3 g.), and phosphorus oxychloride (2·3 g.) was heated on the water-bath for 12 hr., the product treated with aqueous sodium acetate and steam-distilled, and the residue taken up in benzene. The crude aldehyde obtained after evaporation of the solvent was heated at 100° for 5 min. with acetic (10 c.c.) and sulphuric acid (15 c.c.). Basification afforded 3 : 4-benzacridine, which was purified through its picrate and crystallised as almost colourless needles (1·5 g.), m. p. 131°, from ethanol. A similar reaction with di-2-naphthylamine (3 g.), *N*-methylformanilide (3 g.), and phosphorus oxychloride (4 g.) gave 3 : 4-6 : 7-dibenzacridine, pale yellow needles, m. p. 216°, from ethanol–benzene.

1-*Acetyl*-2-*anilinonaphthalene.*—A mixture of 1-acetyl-2-naphthol 15 g.) and aniline (25 g.) was refluxed for 24 hr. with a trace of iodine, the product treated with dilute hydrochloric acid, and the *amino-ketone* taken up in benzene; recrystallisation gave yellow prisms (4 g.), m. p. 115° (benzene) (Found: C, 82·3; H, 6·1; N, 5·1. $C_{18}H_{15}ON$ requires C, 82·7; H, 5·8;

N, 5·3%). Cyclisation with acetic and sulphuric acid, as above, afforded 5-methyl-3 : 4-benzacridine, prisms, m. p. 144° (cf. Postovskii and Lundin, *J. Gen. Chem. U.S.S.R.*, 1940, **19**, 71), in 80% yield.

Reaction of Carbazole with Benzoic Acid and Zinc Chloride.—A mixture of carbazole (10 g.), benzoic acid (10 g.), and fused zinc chloride (20 g.) was heated at 150—155°, and treated according to Bizzari (*loc. cit.*). Distillation *in vacuo* gave recovered carbazole, and 3-benzoylcarbazole (Acheson and Sansom, *loc. cit.*) in 20% yield.

2-(3 : 4-*Dimethylanilino*)-6-*methylnaphthalene.*—A mixture of 3 : 4-dimethylaniline (7 g.) and 6-methyl-2-naphthol (8·3 g.) was heated at 220° with iodine (0·2 g.) for 15 hr., the product taken up in benzene, washed with aqueous sodium hydroxide, and dried (Na_2SO_4), the solvent evaporated, and the residue distilled *in vacuo*, affording 6 g. of a *product*, b. p. 270—272°/18 mm., needles, m. p. 112°, from light petroleum (Found : C, 87·3; H, 7·5. $C_{19}H_{19}N$ requires C, 87·3; H, 7·3%).

The following diarylamines were similarly prepared : N-(p-n-*heptylphenyl*)-2-*naphthylamine* (from 2-naphthol and *p*-*n*-heptylaniline), b. p. 250—260°/19 mm., colourless prisms, m. p. 59°, from light petroleum (Found : C, 87·0; H, 8·6. $C_{23}H_{27}N$ requires C, 87·1; H, 8·5%); N-(p-n-*butylphenyl*)-2-*naphthylamine* (from 2-naphthol and *p*-*n*-butylaniline), colourless needles, m. p. 48°, from light petroleum (Found : C, 87·6; H, 7·6. $C_{20}H_{21}N$ requires C, 87·3; H, 7·6%); N-p-n-*propylphenyl*-2-*naphthylamine* (from 2-naphthol and *p*-*n*-propylaniline), a viscous yellow oil, b. p. 250—260°/15 mm. (Found : C, 87·3; H, 7·2. $C_{19}H_{19}N$ requires C, 87·3; H, 7·3%); 2-(2-*ethyl*-4 : 5-*dimethylphenyl*)-6-*methylnaphthalene* (from 6-methyl-2-naphthol and 2-ethyl-4 : 5-dimethylaniline; Eckert, Buu-Hoï, and Royer, *Compt. rend.*, 1951, **233**, 1461), a viscous yellow oil, b. p. 270°/12 mm. (Found : C, 87·0; H, 8·0. $C_{21}H_{23}N$ requires C, 87·2; H, 8·0%); 2-(4-*ethyl*-2 : 5-*dimethylphenyl*)-6-*methylnaphthalene* (from 6-methyl-2-naphthol and 4-ethyl-2 : 5-dimethylaniline; Eckert, Buu-Hoï, and Royer, *loc. cit.*), b. p. 278—280°/18 mm. (Found : C, 87·3; H, 8·2%); 2-(3-*methyl*-4-n-*octylphenyl*)-6-*methylnaphthalene* (from 6-methyl-2-naphthol and 3-methyl-4-*n*-octylaniline), b. p. 278—280°/10 mm. (Found : C, 86·6; H, 9·3. $C_{28}H_{33}N$ requires C, 86·9; H, 9·2%); 2-(4-*ethyl*-3-*methylphenyl*)-6-*methylnaphthalene* (from 6-methyl-2-naphthol and 4-ethyl-3-methylaniline; Buu-Hoï, Eckert, and Royer, *ibid.*, p. 627), b. p. 278—280°/20 mm. (Found : C, 87·5; H, 7·5. $C_{20}H_{21}N$ requires C, 87·3; H, 7·6%); N-(p-n-*butylphenyl*)-1-*naphthylamine* (from 1-naphthol and *p*-*n*-butylaniline), b. p. 272—274°/20 mm. (Found : C, 87·5; H, 7·9%).

Synthesis of New Benzacridines.—The benzacridines not substituted at position 5 were prepared by the Ullmann–Fetvadjian reaction, and the 5-substituted ones by the modified Bernthsen reaction (cf. Buu-Hoï, *J.*, 1946, 792). All were purified by distillation *in vacuo*, and recrystallised from ethanol.

	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
New **3 : 4-*benzacridines.***						
7-*n*-Propyl-	79°	$C_{20}H_{17}N$	88·5	6·1	88·6	6·3
5-Methyl-7-*n*-propyl- [a]	70	$C_{21}H_{19}N$	88·1	6·9	88·4	6·7
5 : 7 : 8 : 2′-Tetramethyl-	175	$C_{21}H_{19}N$	88·3	6·7	88·4	6·7
7-*n*-Butyl- [b]	91	$C_{21}H_{19}N$	88·5	6·8	88·4	6·7
7-*n*-Heptyl-	80	$C_{24}H_{25}N$	87·9	7·5	88·1	7·6
7-*n*-Butyl-2′-methyl- [c]	87	$C_{22}H_{21}N$	88·1	7·1	88·3	7·0
7-*n*-Butyl-5-methyl-	77	$C_{22}H_{21}N$	88·2	7·3	88·3	7·0
9-Ethyl-5 : 6 : 7 : 2′-tetramethyl- [d]	82	$C_{23}H_{23}N$	88·4	7·5	88·2	7·3
7-Ethyl-5 : 6 : 9 : 2′-tetramethyl-	165	$C_{23}H_{23}N$	88·1	7·5	88·2	7·3
7-Ethyl-5 : 8 : 2′-trimethyl-	167	$C_{22}H_{21}N$	88·5	7·1	88·3	7·0
5 : 8 : 2′-Trimethyl-7-*n*-octyl- [e]	106	$C_{28}H_{33}N$	87·4	8·8	87·7	8·6
7-*n*-Heptyl-5-methyl-	125	$C_{25}H_{27}N$	88·1	7·8	88·0	7·9
New **1 : 2-*benzacridines.***						
7-*n*-Heptyl-	60	$C_{24}H_{25}N$	88·0	7·6	88·1	7·6
7-*n*-Butyl-5-methyl-	104	$C_{22}H_{21}N$	88·0	7·1	88·3	7·0
7-*n*-Butyl- [f]	70	$C_{21}H_{19}N$	88·1	6·9	88·4	6·7

Picrates, m. p. (*a*) 216°, (*b*) 235° (*c*) 244°, (*d*) 220°, (*e*) 215°, (*f*) 214°.

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Synthesis of S-(5′-*Deoxyadenosine*-5′)-*homocysteine, a Product from Enzymic Methylations involving "Active Methionine."*

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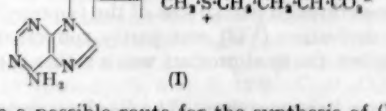
[Reprint Order No. 5941.]

S-(5′-Deoxyadenosine-5′)-homocysteine (II) has been synthesised by reaction of 2′ : 3′-*O*-*iso*propylidene-5′-*O*-toluene-*p*-sulphonyladenosine (IV) and the disodium salt of homocysteine, followed by removal of the *iso*propylidene group with acid. It is identical with a product formed from "active methionine" during enzymic methylations.

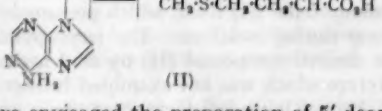
Methylation of the product (II) gives "active methionine" in good yield.

The course of enzymic methylations, in which the methyl group of methionine is transferred to certain substrates, has been clarified considerably by Cantoni (*J. Biol. Chem.*, 1951, **189**, 203; 1951, **189**, 745; *J. Amer. Chem. Soc.*, 1952, **74**, 2942; "Phosphorus Metabolism," 1952, Vol. II, 129). The sequence of events is illustrated here in the typical case of the formation of creatine from guanidinoacetic acid. Methionine reacts with adenosine triphosphate (ATP) in the presence of an enzyme to give "active methionine" and three mols. of inorganic phosphate. "Active methionine" then donates a methyl group to guanidinoacetic acid in the presence of a second enzyme, with the formation of creatine. Until recently, however, the fate of the "active methionine" molecule was uncertain.

The formulation of "active methionine" as the sulphonium compound (I) (Cantoni, *J. Amer. Chem. Soc.*, 1952, **74**, 2942; *J. Biol. Chem.*, 1953, **204**, 403) has been confirmed by further degradation studies (Baddiley, Cantoni, and Jamieson, *J.*, 1953, 2662) and by a total synthesis (Baddiley and Jamieson, *J.*, 1954, 4280). Consequently, it has been suggested that the primary product resulting from the transmethylation reactions involving "active methionine" should be *S*-(5′-deoxyadenosine-5′)-homocysteine (II) (Woolley, *Nature*, 1953, **171**, 323; Baddiley, Cantoni, and Jamieson, *loc. cit.*; Challenger, *Endeavour*, 1953, **12**, 173). This has now been confirmed by the isolation of this primary product from an enzymic system in which "active methionine" effects the methylation of guanidinoacetic acid (Cantoni and Scarano, *J. Amer. Chem. Soc.*, 1954, **76**, 4744) and by its identification with a sample of synthetic *S*-(5′-deoxyadenosine-5′)-homocysteine prepared by the methods described here.



(I)



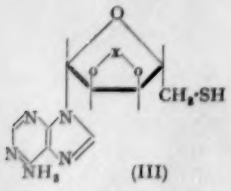
(II)

In a possible route for the synthesis of (II) we envisaged the preparation of 5′-deoxy-5′-mercapto-2′ : 3′-*O*-*iso*propylideneadenosine (III) and subsequent reaction of this with α-amino-γ-bromobutyric acid, followed by hydrolysis of the *iso*propylidene residue. The mercapto-derivative (III) of adenosine was prepared in rather low yield by heating together 2′ : 3′-*O*-*iso*propylidene-5′-*O*-toluene-*p*-sulphonyladenosine and potassium thiolacetate under conditions similar to those adopted by Chapman and Owen (*J.*, 1950, 579) for the conversion of toluene-*p*-sulphonyl esters into esters of thiolacetic acid. The acetyl group was removed readily by the action of methanolic ammonia.

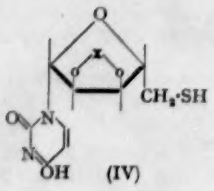
In view of the difficulties encountered in the preparation of useful amounts of the thiol (III), experiments were performed on uridine derivatives. One of the main side reactions in the adenosine series, *cyclo*nucleoside formation, does not occur readily with uridine derivatives. 2′ : 3′-*O*-*iso*Propylidene-5′-*O*-toluene-*p*-sulphonyluridine reacted smoothly

with potassium thiolacetate and the resulting thiolacetate was deacetylated to the thiol (IV), in 88% overall yield. However, attempts to prepare a mixed sulphide from (IV) and α-amino-γ-bromobutyric acid hydrobromide or γ-bromo-α-formamidobutyric acid were unsuccessful.

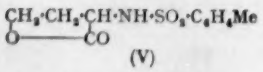
It is possible that the acidic nature of uridine and its derivatives was responsible in part for our failures in this route. This is supported by the observation that 5′-deoxy-5′-mercapto-2′ : 3′-*O*-*iso*propylideneadenosine (III), when heated with methyl γ-bromo-α-formamidobutyrate and then subjected to cautious acid and alkaline hydrolysis, yielded traces of a product with the properties expected for *S*-(5′-deoxyadenosine-5′)-homocysteine (II).



(III)



(IV)



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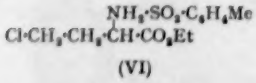
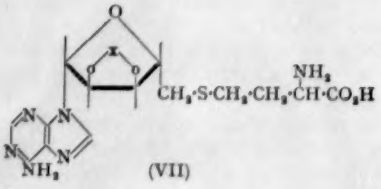


(VI)



(VII)

X = CMe_2.

The low yield and multiplicity of products in the above synthesis might have arisen in the attempted removal of the formyl group. Toluene-*p*-sulphonyl groups, on the other hand, can be removed readily from amino-compounds with sodium in liquid ammonia. A modified synthesis adopting this feature was attempted. α-Toluene-*p*-sulphonamido-γ-butyrolactone (V) was converted into ethyl γ-chloro-α-toluene-*p*-sulphonamidobutyrate (VI) by the action of dry hydrogen chloride in ethanol. This reacted readily with sodium ethyl sulphide and then yielded ethionine on hydrolysis. The chloro-ester (VI) was heated in dimethylformamide with the sodium derivative of the thiol (III); the resulting ester was hydrolysed with dilute alkali and then treated with sodium in liquid ammonia. Paper chromatography of the product indicated that it was a mixture. However, one spot corresponded with that given by *S*-(5-deoxy-2′ : 3′-*O*-*iso*propylideneadenosine-5′)-homocysteine (VII) (see below). One of the contaminants was *S*-(5′-deoxyadenosine-5′)-homocysteine (II) itself, which presumably arose through partial loss of the *iso*propylidene group during isolation. The *iso*propylidene derivative (VII) was partly converted into the desired compound (II) by acid hydrolysis but the final product was a rather complex mixture which was not examined further.

A much more satisfactory synthesis starts from homocysteine. The disodium derivative of homocysteine, prepared in liquid ammonia, was allowed to react with 2′ : 3′-*O*-*iso*propylidene-5′-toluene-*p*-sulphonyladenosine either in liquid ammonia at a low temperature or in dimethylformamide at 100°, the product (VII) being obtained as a white solid after removal of toluene-*p*-sulphonate and sodium ions on ion-exchange resins. The *iso*propylidene group in (VII) was rather resistant towards acid hydrolysis. Paper chromatography showed that, under conditions which usually effect complete hydrolysis of *iso*propylidene derivatives of adenosine, not more than about 50% removal had occurred from (VII). More prolonged reaction, however, led to complete hydrolysis and a good yield of crystalline *S*-(5′-deoxyadenosine-5′)-homocysteine.

The synthetic substance was compared by paper chromatography with material isolated by Cantoni and Scarano (*loc. cit.*) from an enzyme system in which "active

methionine " had effected methylation of guanidinoacetic acid. Both substances had the same R_F in several solvent systems, absorbed ultra-violet light at 260 mμ, and gave positive reactions on the paper with the periodate–Schiff, ninhydrin, and iodoplatinate spray reagents. We conclude that the two substances are identical, and hence that the primary enzymic demethylation product formed from " active methionine " is correctly represented as (II). The subsequent fate of this product in biological systems is uncertain but it is hoped that the solution of this problem may be facilitated by the availability of synthetic *S*-(5′-deoxyadenosine-5′)-homocysteine.

Methylation of *S*-(5′-deoxyadenosine-5′)-homocysteine with methyl iodide gave an excellent yield of " active methionine." This not only confirms the structure of the synthetic material but also provides a convenient route for the preparation of quantities of " active methionine."

Experimental

*5′-Deoxy-5′-mercapto-2′ : 3′-*O*-iso**propylideneadenosine** (III).—A solution of **2′ : 3′-*O*-iso**propylidene-5′-*O*-toluene-*p*-sulphonyladenosine (5·2 g.) (cf. Baddiley and Jamieson, *loc. cit.*) and dry potassium thiolacetate (6 g.) in alcohol–acetone (50 c.c.; 1 : 1) was refluxed for 3 hr. Solid was filtered off and washed with acetone, then the filtrate and washings were evaporated to dryness *in vacuo*. The residue was dissolved in chloroform and washed with a little water, and solvent was removed *in vacuo*. The impure acetyl derivative was dissolved in methanol (50 c.c.), and the solution was saturated at room temperature with dry ammonia. After 10 min. the solvent was evaporated and the partly crystalline residue was washed with a little cold alcohol. The *mercapto-compound* had m. p. 186—189° (Found: C, 48·0; H, 5·2; N, 21·7; S, 10·3. $C_{13}H_{17}O_3N_5S$ requires C, 48·2; H, 5·2; N, 21·6; S, 9·9%).

*2′ : 3′-*O*-iso**Propylideneuridine**.—Levene and Tipson (*J. Biol. Chem.*, 1934, **106**, 113) report m. p. 159—160° for this substance. Our material, prepared in a similar manner, had m. p. 162°.

*2′ : 3′-*O*-iso**Propylidene-5′-toluene-**p**-sulphonyluridine**.—This compound was obtained as a resin by Levene and Tipson (*loc. cit.*). It was found here that, after being boiled with ether, the toluene-*p*-sulphonyl derivative formed well-defined crystals (17 g. from 17 g. of the *iso*propylidene compound). Recrystallised from acetone–ether containing a little light petroleum (40—60°) it had m. p. 150°.

*5′-Deoxy-5′-mercapto-2′ : 3′-*O*-iso**propylideneuridine** (IV).—This was prepared from the above toluenesulphonyl derivative (4·4 g.) and potassium thiolacetate (2·2 g.) in acetone (100 c.c.) as described above for the adenosine compound. Fine needles of the *mercapto-compound* were formed during the treatment with methanolic ammonia. These were filtered off after concentration of the solution, then washed with ether. Recrystallised from methanol–ethanol (1 : 1) they had m. p. 200—215° (2·5 g., 88%) (Found: C, 48·0; H, 5·2; N, 9·7; S, 11·5. $C_{13}H_{16}O_5N_2S$ requires C, 47·4; H, 5·3; N, 9·4; S, 10·7%).

*α-Toluene-*p*-sulphonamido-γ-butyrolactone* (V).—Toluene-*p*-sulphonyl chloride (5 g.) was shaken with a suspension of α-amino-γ-butyrolactone hydrobromide (4·5 g.) in dry pyridine (50 c.c.) at room temperature overnight. Pyridine was removed *in vacuo*, a little water was added, and the mixture was extracted with 3 lots of chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. Recrystallisation of the residue from water gave white prisms (4·2 g.) of the *toluene-*p*-sulphonyl derivative*, m. p. 108—110° (Found: N, 5·4; S, 12·9. $C_{11}H_{13}O_4NS$ requires N, 5·7; S, 13·1%).

*Ethyl γ-Chloro-α-toluene-*p*-sulphonamidobutyrate* (VI).—A solution of the above toluene-*p*-sulphonyl derivative (1 g.) in alcohol (30 c.c.) was saturated with dry hydrogen chloride at room temperature and set aside overnight. Solvent was removed *in vacuo* and the residue was recrystallised from light petroleum. The *chloro-ester* (0·8 g.) had m. p. 65—67° (Found: C, 49·3; H, 5·8; N, 4·7; Cl, 10·4. $C_{13}H_{18}O_4NSCl$ requires C, 48·8; H, 5·6; N, 4·4; Cl, 10·9%).

Ethionine.—Ethanethiol (0·26 g.) was added to a solution of sodium (0·09 g.) in alcohol (25 c.c.), and the solution was evaporated to about 10 c.c. Dimethylformamide (25 c.c.) was then added, followed by a solution of the above chloro-ester (0·63 g.) in dimethylformamide (25 c.c.), and the mixture was heated at 100° for 3 hr. Solvent was removed *in vacuo* and the residue was extracted with 3 lots of chloroform. Chloroform was evaporated and the residue was heated under reflux for 20 min. in N-sodium hydroxide (20 c.c.). The solution was then passed down a column of Amberlite IRC-50 resin (H^+ form) to remove sodium ions and concentrated *in vacuo* to a light oil. This was dissolved in liquid ammonia (20 c.c.), and

sodium was added until a blue colour persisted. Ammonia was allowed to evaporate and the resulting solid was dissolved in water and passed through a column of Amberlite IR-120 (ammonium form). After concentration the eluate was passed through a column of Amberlite IR-4B (hydroxyl form) to remove toluene-*p*-sulphonic acid. The eluate was evaporated to dryness and the crystalline product was washed with alcohol and recrystallised from aqueous alcohol. Ethionine (0·04 g.) had m. p. 235° (decomp.) and R_F 0·51 in butanol–acetic acid–water, indistinguishable from that of an authentic sample.

S-(5′-*Deoxyadenosine*-5′)-*homocysteine* (II).—*Method* 1. To a solution of γ-bromo-α-formamidobutyric acid (1·7 g.) (Baddiley and Jamieson, *loc. cit.*) in dry methanol was added an excess of freshly distilled ethereal diazomethane. Solvent was removed *in vacuo*, leaving a clear yellow oil. Sodium was added in small pieces to a solution of the mercaptoadenosine derivative (III) (0·6 g.) in liquid ammonia until the blue colour persisted. Ammonia was evaporated *in vacuo* and dry dimethylformamide (5 c.c.) was added followed by a solution of the above methyl ester of γ-bromo-α-formamidobutyric acid (0·45 g.) in dimethylformamide (10 c.c.). The mixture was heated for 3 hr. at 100° under nitrogen. Solvent was removed *in vacuo*, a little water was added, and the solution was extracted with 3 lots of chloroform. The aqueous layer was acidified and re-extracted with chloroform, then the combined organic extracts were evaporated to dryness *in vacuo*. The residue was heated under reflux in 0·1N-sodium hydroxide (5 c.c.) for 3 min. The resulting solution was passed through a column of Amberlite IR-120 resin (H^+ form), the column was washed well with water, and the products were eluted with a large volume of ammonia [equal parts of ammonia (*d* 0·88) and water]. The eluate was evaporated to dryness *in vacuo*. Paper chromatography of the product showed the presence of several components. One of these components had R_F 0·69 in butanol–acetic acid–water, absorbed ultra-violet light, and gave a positive test for a sulphide with the iodoplatinate spray and negative tests with ninhydrin and periodate–Schiff reagents. This was probably the formyl derivative of (VII). A faint spot, R_F 0·08, gave positive ninhydrin and periodate–Schiff tests and was probably the desired homocysteine derivative (II), arising by hydrolysis of the formyl derivative on the column. However, in view of the complex nature of the mixture, suitable conditions for the hydrolysis of the formyl derivative of (VII) to (II) were not determined.

Method 2. A solution of ethyl γ-chloro-α-toluene-*p*-sulphonamidobutyrate (VI) (0·9 g.) in dry dimethylformamide (50 c.c.) was added to the dry, freshly prepared sodium derivative of the mercaptoadenosine compound (III) (0·87 g.). The resulting solution was heated at 100° for 1 hr. during which some solid was deposited. Alkaline hydrolysis of the ester, removal of the toluene-*p*-sulphonyl group, and isolation of the product were carried out as described in the ethionine synthesis above. The expected product at this stage is the *iso*propylidene derivative (VII). In fact, the product was not homogeneous but one component, R_F 0·3 in butanol–acetic acid–water, had the properties expected for this substance. It absorbed ultra-violet light and gave positive reactions with ninhydrin and iodoplatinate spray reagents and a negative reaction with the periodate–Schiff reagent. It had the same R_F as the authentic *iso*propylidene compound (VII) prepared by the method described below. A small amount of S-(5′-deoxyadenosine-5′)-homocysteine (II) was also present, the amount being increased by acid hydrolysis as described in Method 3.

Method 3. Sodium (0·46 g.) was added to a solution of homocysteine (1·36 g.) in liquid ammonia (50 c.c.), and then a solution of freshly prepared 2′ : 3′-*O*-*iso*propylidene-5′-*O*-toluene-*p*-sulphonyladenosine (from 4·6 g. of 2′ : 3′-*O*-*iso*propylideneadenosine) in liquid ammonia (50 c.c.). Moisture was excluded by a sodium hydroxide tube and solvent was allowed to evaporate. The residue was dissolved in water and unchanged homocysteine (0·1 g.) was filtered off. The filtrate was passed through a column of Amberlite IR-120 (ammonium form) to remove sodium ions, and the eluate was concentrated *in vacuo* and passed through a column of Amberlite IR-4B (hydroxyl form) to remove toluene-*p*-sulphonate ions. The eluate from the second column was evaporated to dryness *in vacuo*, leaving a solid residue of S-(5′-*deoxy*-2′ : 3′-O-iso*propylideneadenosine*-5′)-*homocysteine* (VII), R_F 0·3 in butanol–acetic acid–water, R_F 0·61 in *n*-propanol–ammonia–water. This substance absorbed ultra-violet light and gave positive reactions with ninhydrin and iodoplatinate spray reagents and a negative periodate–Schiff reaction. The only detectable impurity was a small amount of homocysteine. The *iso*propylidene residue was removed by hydrolysis in N-sulphuric acid (16 c.c.) at room temperature for 36 hr. Sulphuric acid was removed by addition of the calculated amount of barium hydroxide solution, and barium sulphate was then removed by filtration through Supercel silica and was washed well with water. The combined filtrate and washings were evaporated

to dryness *in vacuo* and the residue was recrystallised from aqueous alcohol. *S*-(5′-Deoxyadenosine-5′)-homocysteine (II) (520 mg.) formed small small prisms, m. p. 190—193° (decomp.) raised by several recrystallisations to 204° (decomp.). It gave a *picrate*, m. p. 170° (decomp.) (Found: C, 37·6; H, 3·9; N, 20·4; S, 4·6. $C_{20}H_{23}O_{12}N_9S,H_2O$ requires C, 38·0; H, 3·9; N, 19·9; S, 5·1%). The synthetic and the natural material were indistinguishable in R_F and chemical reactions on paper. In butanol–acetic acid–water both had R_F 0·08, and in *n*-propanol–ammonia–water R_F 0·38.

S-(5′-*Deoxyadenosine-5′*)-*methionine* (*Active Methionine*) (I).—The above derivative (II) (186 mg.) was dissolved in acetic acid (2 c.c.), and methyl iodide (0·5 c.c.) was added. The tube was sealed and kept at room temperature in the dark for 6 days. Solvent was removed at room temperature *in vacuo* and the resulting gum was dissolved in 0·1N-hydrochloric acid (3 c.c.). To this solution was added a saturated aqueous solution of Reinecke salt (adjusted to pH 2 with hydrochloric acid) until precipitation was complete. The precipitated salt (*ca.* 350 mg.) was shaken in dry acetone with silver sulphate (0·5 g.) at room temperature for 24 hr. Solid material was removed by filtration and washed with warm methanol. The combined filtrates were evaporated to dryness *in vacuo*. Chromatography of the residue in butanol–acetic acid–water showed the presence of a single ultra-violet-absorbing spot which did not move from the origin. This was indistinguishable from natural active methionine when examined by the spray reagents described by Baddiley and Jamieson (*loc. cit.*). A sample was heated in water at 90° for 2 hr. and re-examined by paper chromatography: like natural active methionine, it was converted in this way into 5′-deoxy-5′-methylthioadenosine, R_F 0·70 in butanol–acetic acid–water.

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Quinones. Part V. The Chemistry of Naphthazarin.*

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The synthesis, reduction, and addition reactions of naphthazarin and its derivatives have been investigated, and the structures of several known compounds elucidated.

AT least a dozen quinones related to naphthazarin (5 : 8-dihydroxy-1 : 4-naphthaquinone) occur in Nature. In several cases the structure is not known completely, *e.g.*, of javanicin (Arnstein and Cook, *J.*, 1947, 1021), fusarubin (Ruelius and Gauhe, *Annalen*, 1950, **569**, 38), and some of the echinochromes and spinochromes (see Goodwin and Srisukh, *Biochem. J.*, 1950, **47**, 69); few of these quinones have been synthesised. As a preliminary to synthetical work in this field we have explored the methods available for the preparation of naphthazarins. Although, in principle, any substituted naphthazarin can be built up in stages starting from a suitable benzenoid compound (cf., *e.g.*, Brunner and Singule, *Monatsh.*, 1948, **79**, 81) the usual procedure is laborious and more direct methods are desirable. Again, the direct introduction of substituents into naphthazarin by the standard addition reactions would be advantageous but appears to be difficult: *e.g.*, addition of acetic anhydride requires ten days (Dimroth and Roos, *Annalen*, 1927, **456**, 191) and the addition of amines is also slow and requires a large excess (Fierz-David and Stockar, *Helv. Chim. Acta*, 1943, **26**, 92). We have therefore also examined the behaviour of naphthazarin in some common addition reactions.

Naphthazarin was first obtained by Roussin (*Compt. rend.*, 1861, **52**, 1033) by the action of sulphur and fuming sulphuric acid on 1 : 5-dinitronaphthalene. This reaction was formerly used on a commercial scale but has not been applied to the preparation of homologues of naphthazarin, indeed Kuroda and Wada (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1938, **34**, 1740) failed to obtain methylnaphthazarin by this method. We have,

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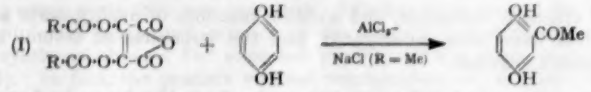
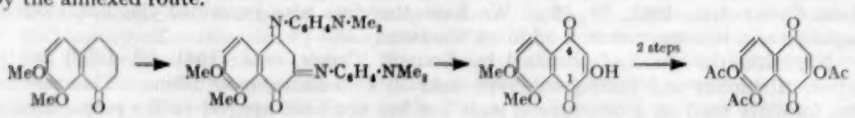
however, obtained a small yield of methylnaphthazarin from 2-methyl-1 : 5-dinitronaphthalene, and 2 : 6-dimethyl- and 2 : 6-dichloro-naphthazarin were obtained in the same way from the appropriate dinitro-compounds. Although the yields are low and the method is restricted by the inaccessibility of suitable 1 : 5-dinitronaphthalenes it is the most direct procedure for preparing 2 : 6-dialkylnaphthazarins. The formation of naphthazarin from 1 : 8-dinitronaphthalene by reaction with fuming sulphuric acid and reducing agents other than sulphur (*e.g.*, aniline, phenylhydrazine, tin) has been claimed (G.P. 79,406, 76,922) but Fierz-David and Stockar (*loc. cit.*) found the yield to be very poor and we have not investigated this route.

The most general synthesis of naphthazarins is the condensation of quinols with maleic anhydrides in fused sodium chloride–aluminium chloride (Zahn and Ochwat, *Annalen*, 1928, **462**, 72). Most known naphthazarins have been made by this means and some further examples are recorded in the Experimental section, but the method is not suitable for the synthesis of naphthazarins containing one substituent in each ring, or two substituents in one ring and one in the other, since mixtures result which are difficult to separate. Thus toluquinol and citraconic anhydride afforded a mixture of 2 : 6- and 2 : 7-dimethylnaphthazarin (Kuroda, *Proc. Imp. Acad. Tokyo*, 1939, **15**, 226). The severity of the reaction conditions is also a limiting factor as Weiss and Nord (*Arch. Biochem.*, 1950, **22**, 228) found in the attempted condensation of maleic anhydride with 2 : 5-dimethoxyphenylacetone. The most complex naphthazarin synthesised to data, echinochrome A, was obtained by Wallenfels and Gauhe (*Ber.*, 1943, **76**, 325) by condensing 2-ethyl-1 : 3 : 4-trimethoxybenzene with dibenzoyloxymaleic anhydride. The yield in this case was only 1% owing to the instability of the anhydride component. As a number of naphthazarins found in Nature contain two hydroxyl groups in the 2 : 3(or 6 : 7)-positions we attempted the similar condensation of diacetoxymaleic anhydride with quinol. No naphthazarin derivative could be detected, the principal product being 2 : 5-dihydroxyacetophenone. The corresponding condensation with dibenzoyloxymaleic anhydride gave 2 : 5-dihydroxybenzophenone. It is evident from the structure of the diesters (I) that three oxygen atoms can co-ordinate with aluminium chloride with almost equal facility and the preponderant formation of acetyl or benzoyl cations would be expected.



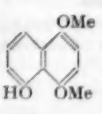
As a variety of substituted juglones (5-hydroxy-1 : 4-naphthaquinone) of known orientation are readily available (Thomson, *J. Org. Chem.*, 1948, **13**, 377, 870; 1951, **16**, 1082) methods for converting these into the corresponding naphthazarins were explored, but without success. Direct oxidation of juglone with lead tetra-acetate and with Fremy's salt yielded no naphthazarin. Oxidation by the Elbs persulphate method was also unprofitable. As juglone itself is not stable in alkaline solution the reaction was tried with 3-hydroxy-, 2-chloro-3-hydroxy-, and 2 : 6-dibromo-3-hydroxy-juglone. Oxidation products were isolated in very low yield from the first two but all the bromoquinone was recovered unchanged. The crude product obtained from 3-hydroxyjuglone gave an acetyl derivative which was not 5 : 6 : 8- or 2 : 7 : 8-triacetoxy-1 : 4-naphthaquinone : it has not been identified. A comparable persulphate oxidation of 1-hydroxyanthraquinone yielded a trace of quinizarin. 2 : 7 : 8-Triacetoxy-1 : 4-naphthaquinone was synthesised by the annexed route.



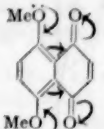
A dimethoxynaphthol, regarded as (II), was obtained by Ruelius and Gauhe (*Annalen*, 1951, **571**, 69) from juglone acetate by catalytic reduction and subsequent methylation and hydrolysis. Its conversion into naphthazarin dimethyl ether and final demethylation

would constitute a straightforward synthesis of naphthazarin from juglone. Efforts to obtain naphthazarin dimethyl ether from Ruelius and Gauhe's naphthol were fruitless and indicated that the structure (II) was incorrect (see Hayes and Thomson, *J.*, 1955, 904).

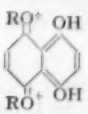
The reaction of naphthazarin with the following reagents was examined: chlorine, aniline, toluene-*p*-thiol, toluene-*p*-sulphinic acid, potassium hydrogen sulphite, hydrochloric acid, and hydrocyanic acid. In general it was found that naphthazarin was a relatively unreactive quinone. The addition of chlorine and aniline was very slow, hydrochloric acid failed to react, and no definite compound could be isolated from the crude black product resulting from the reaction with hydrocyanic acid (cf. Marschalk, *Bull. Soc. chim. Fr.*, 1935, **2**, 1809). On the other hand toluene-*p*-sulphinic acid, toluene-*p*-thiol, and potassium hydrogen sulphite reacted normally, the last two yielding diaddition products, which again suggests that these compounds add by a radical mechanism (cf. Thomson, *J. Org. Chem.*, 1951, **16**, 1082; Lyons and Thomson, *J.*, 1953, 2910). Fieser and Dunn (*J. Amer. Chem. Soc.*, 1937, **59**, 1016) observed that naphthazarin diacetate took part in Diels–Alder reactions much more rapidly than did naphthazarin itself. It has also been shown that the addition reactions of juglone are different from those of its acetate (Thomson, *loc. cit.*) and its methyl ether (McLeod and Thomson, unpublished work). Naphthazarin diacetate and dimethyl ether reacted normally with toluene-*p*-thiol. Chlorine reacted rapidly with the dimethyl ether and slowly with the diacetate (but faster than with naphthazarin itself). Both compounds failed to react with aniline. The addition of acetic anhydride to naphthazarin diacetate is very slow, as already mentioned, and the dimethyl ether did not react at all under the same conditions. An attempt to form the oxide of the dimethyl ether, by use of hydrogen peroxide, gave 2-hydroxy-5 : 8-dimethoxy-1 : 4-naphthaquinone. It is again evident that esterification and etherification of *peri*-hydroxyl groups has a marked effect on the additive powers of a naphthaquinone.



(II)



(III)



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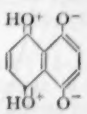
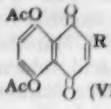


(V)

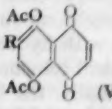
It is clear that in naphthazarin dimethyl ether (III) conjugation of the methoxyl groups with the carbonyl groups will reduce the reactivity of the 2 : 3-double bond towards nucleophilic reagents (*e.g.*, aniline) and increase the reactivity towards electrophilic reagents (*e.g.*, chlorine) and that *peri*-acetoxy-groups will have a similar, but weaker, effect. The failure of naphthazarin dimethyl ether to take part in acid-catalysed Thiele acetylation can be ascribed to salt formation, the catalyst giving rise to structures such as (IV; R = Me). (Naphthazarin dimethyl ether can be extracted from organic solvents with concentrated hydrochloric acid.) In the past, the tautomeric nature of naphthazarin has been emphasised but it is evident that its general stability, intense colour, strong hydrogen-bonding, and low chemical reactivity are due to the importance of resonance structures of the type (V) which lower the quinonoid activity of the molecule. The stability of the dianion of naphthazarin is most striking; the deep cornflower-blue solution in aqueous sodium hydroxide is stable for days and naphthazarin is recovered unchanged on acidification. This is a most unusual property for a naphthaquinone lacking a hydroxyl group in the quinonoid ring. Palacios and Salvia (*Anales Fis. Quim.*, 1934, **32**, 49) have shown by *X*-ray analysis that the naphthazarin molecule has a centre of symmetry and we did consider earlier that the hydrogen bonds might be symmetrical. This in fact has been proposed by Josien, Fuson, Lebas, and Gregory (*J. Chem. Phys.*, 1953, **21**, 331). However, a preliminary infra-red examination of dideuterated naphthazarin, kindly undertaken by Dr. T. S. Robinson, did not support this hypothesis and a fuller investigation by Hadži and Sheppard (*Trans. Faraday Soc.*, 1954, **50**, 911) has established the asymmetry of the hydrogen bonds.

Most of the new naphthazarins described in this paper have been reduced with acid

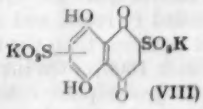
stannous chloride, to give β-hydronaphthazarin (1 : 2 : 3 : 4-tetrahydro-5 : 8-dihydroxy-1 : 4-dioxonaphthalene) and its derivatives. The only new observation (cf. Bruce and Thomson, *J.*, 1952, 2759) is that whereas chlorine atoms are normally eliminated during this reaction (see p. 1096) this is not the case with 3-chloro-2-methylnaphthazarin : a new diketone, 6-chloro-1 : 2 : 3 : 4-tetrahydro-5 : 8-dihydroxy-7-methyl-1 : 4-dioxonaphthalene, was obtained. This enabled us to establish the structure of methylnaphthazarin diacetate.



(VI)

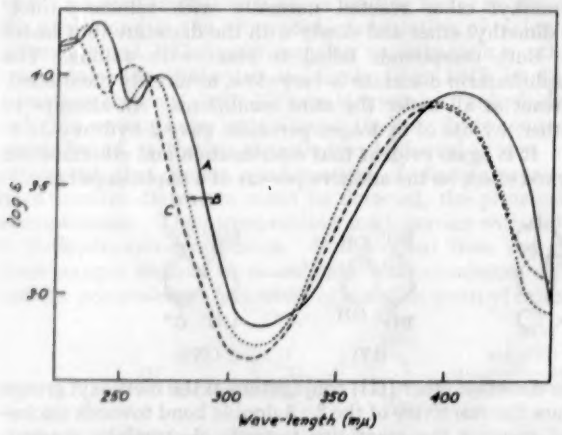


(VII)



(VIII)

There are two possible structures for the esters of substituted naphthazarins, (VI) or (VII). Fieser and Dunn (*loc. cit.*) have shown that naphthopurpurin triacetate has structure (VII; R = AcO) whereas methylnaphthazarin diacetate we find has structure (VI; R = Me). Addition of chlorine to methylnaphthazarin diacetate gave a dichloride which readily eliminated hydrochloric acid to form a chloromethylnaphthazarin diacetate. Hydrolysis



A, Naphthazarin–$KHSO_3$ adduct.
B, 1 : 2 : 3 : 4-*Tetrahydro-5* : 8-*dihydroxy-6-methyl-1* : 4-*dioxonaphthalene.*
C, 1 : 2 : 3 : 4-*Tetrahydro-5* : 8-*dihydroxy-1* : 4-*dioxonaphthalene.*

of the latter and reduction of the quinone obtained with acid stannous chloride did not eliminate the halogen atom. Since chlorine is lost by reduction of 6- and 7-chloro-2-methylnaphthazarin it follows that the chlorine atom and the methyl group must both lie in the same, *i.e.*, the quinonoid, ring of the above chloromethylnaphthazarin diacetate. Hence methylnaphthazarin diacetate must have structure (VI; R = Me). Ozonolysis of methylnaphthazarin diacetate leads to the same conclusion (Raudnitz and Behrens, *Ber.*, 1935, **68**, 1485). Chloronaphthazarin diacetate has also structure (VI; R = Cl). This is established by addition of chlorine to naphthazarin diacetate followed by elimination of hydrochloric acid from the resulting dichloride. The chloronaphthazarin diacetate obtained is identical with that produced by acetylation of chloronaphthazarin.

We have investigated the structure of the addition product of naphthazarin and potassium hydrogen sulphite (see p. 1091). A water-soluble bisulphite compound of naphthazarin, Alizarin Black S (C.I. No. 1019) was at one time used for printing. It was described as a dark brown powder (G.P. 41,518) and was apparently regarded as a normal carbonyl bisulphite compound. We find that the purified material is light yellow, and both acid and alkaline hydrolysis failed to liberate naphthazarin. The compound must therefore be formed by the usual quinonoid 1 : 4-addition. It is too stable to be a derivative of 1 : 4 : 5 : 8-tetrahydroxynaphthalene and its colour, behaviour in alkaline solution and ultra-violet absorption spectrum (see Figure) indicate structure (VIII). One objection is that, although reduction with acid stannous chloride gives a bright yellow solution,

β-hydronaphthazarin is not formed. It may be that the sulphonic acid group is eliminated only from the reduced ring, subsequent reduction and tautomerisation giving β-hydronaphthazarin-6-sulphonic acid (cf. Bruce and Thomson, *loc. cit.*).

Experimental

2-Methylnaphthazarin.—To a suspension of 2-methyl-1 : 5-dinitronaphthalene (3·5 g.) in 100% sulphuric acid (16·5 g.) was added a mixture of sulphur (1·75 g.) and fuming sulphuric acid (66% of SO_3; 26·3 g.) with constant stirring, the temperature being kept below 30°. After 1 hr. the mixture was poured on crushed ice (400 g.) with vigorous stirring, a bright blue solution being obtained. This was filtered and boiled for 1 hr. The blue colour disappeared and a reddish-brown precipitate formed. This was collected, dried, and sublimed in a high vacuum at 150°. The greenish crystalline sublimate, m. p. 167—170°, crystallised from alcohol as bright green plates, m. p. 173° not depressed on admixture with methylnaphthazarin.

2 : 6-*Dimethylnaphthazarin.*—To a suspension of 2 : 6-dimethyl-1 : 5-dinitronaphthalene (4 g.) in 100% sulphuric acid (67 g.) was added gradually with stirring a mixture of sulphur (1·2 g.) and fuming sulphuric acid (60% of SO_3; 20 g.) at <40°. The mixture was set aside for 1½ hr. at room temperature and then poured on crushed ice (500 g.). The bright blue solution was filtered and boiled until the colour had changed to red. A red precipitate formed on cooling. The suspension was extracted with chloroform which in turn was repeatedly extracted with 2N-sodium hydroxide until no further blue colour appeared in the aqueous layer. The combined alkaline extracts were acidified with dilute sulphuric acid and the red precipitate thus obtained was collected, dried, and sublimed in a high vacuum at 170°, forming dark red needles with a green sheen having no m. p. (decomp. >200°) (1 g.). 2 : 6-*Dimethylnaphthazarin* crystallised from light petroleum (b. p. 100—120°) in green needles (Found : C, 65·6; H, 4·7. $C_{12}H_{10}O_4$ requires C, 66·0; H, 4·6%). Acetic anhydride and a trace of concentrated sulphuric acid in the cold afforded the *monoacetate* which crystallised from alcohol or light petroleum in orange needles, m. p. 150° (Found : C, 64·6; H, 4·7. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·65%). Acetylation in the same way, but with heating, gave the *diacetate* which formed yellow needles, m. p. 161° (from alcohol) (Found : C, 63·1; H, 4·55. $C_{16}H_{14}O_6$ requires C, 63·55; H, 4·65%).

2 : 6-*Dichloronaphthazarin.*—To a suspension of 2 : 6-dichloro-1 : 5-dinitronaphthalene (1·6 g.) in 100% sulphuric acid (25 g.) was added a mixture of sulphur (0·5 g.) and fuming sulphuric acid (60% of SO_3; 8 g.) at <30°. After 1½ hr. the mixture was poured on crushed ice (150 g.), forming a blue solution and a blue precipitate. The latter was filtered off and washed with concentrated hydrochloric acid, and the combined filtrate and washings were boiled until the blue colour had changed to red. The red precipitate formed on cooling was dried (0·3 g.), dissolved in chloroform, and shaken with activated alumina which rapidly became blue. The alumina was filtered off, washed with chloroform, and extracted with hot glacial acetic acid. Dilution of the extract with water gave a red *quinone* which crystallised from light petroleum (b. p. 100—120°) as almost black needles with a green sheen which had no m. p. (decomp. *ca.* 240°) (5%) (Found : C, 46·0; H, 1·5; Cl, 27·0. $C_{10}H_4O_4Cl_2$ requires C, 46·3; H, 1·55; Cl, 27·3%). The *diacetate* separated from light petroleum in yellow needles, m. p. 208° (Found : C, 49·3; H, 2·2; Cl, 20·0. $C_{14}H_8O_6Cl_2$ requires C, 49·0; H, 2·35; Cl, 20·6%).

2 : 3-*Dichloronaphthazarin.*—To a fused mixture of sodium chloride (20 g.) and anhydrous aluminium chloride (100 g.) at 180° was added a mixture of maleic anhydride (10 g.) and 2 : 3-dichloroquinol (18 g.) with constant stirring. The temperature was kept at 180° till evolution of hydrogen chloride had ceased and the melt then allowed to cool. After decomposition with dilute hydrochloric acid the red precipitate of *quinone* obtained was collected, dried, and crystallised from light petroleum in scarlet plates, m. p. 192° (30%) (Found : C, 46·1; H, 1·6. $C_{10}H_4O_4Cl_2$ requires C, 46·3; H, 1·55%). The *diacetate* crystallised from acetone in yellow needles, m. p. 233° (Found : C, 49·1; H, 2·3. $C_{14}H_8O_6Cl_2$ requires C, 49·0; H, 2·35%).

6- *and* 7-*Chloro*-2-*methylnaphthazarin.*—Chloroquinol and citraconic anhydride were condensed as above. The product crystallised from alcohol in red needles with a green sheen, melting range 155—165° indicating a mixture of two isomers (Found : C, 55·25; H, 2·7. Calc. for $C_{11}H_7O_4Cl$: C, 55·4; H, 2·95%).

Condensation of Quinol with Diacetoxymaleic Anhydride.—To a mixture of sodium chloride (4 g.) and anhydrous aluminium chloride (20 g.) at 120° was added gradually with stirring a mixture of quinol (0·8 g.) and diacetoxymaleic anhydride (1 g.). The temperature was raised to 180° for a few minutes and the mixture then allowed to cool. The product was decomposed

in the usual way with dilute hydrochloric acid and the mixture boiled for 2 min. After cooling and filtration, the residue and solution were extracted with chloroform. Evaporation of the solvent left an orange solid which crystallised from light petroleum (b. p. 100—120°) in pale yellow needles, m. p. 201° (0·5 g.) (Found : C, 63·15; H, 5·45. Calc. for $C_8H_6O_3$: C, 63·15; H, 5·3%). The compound formed a diacetate, m. p. 67·5° (Found : C, 61·0; H, 5·25. Calc. for $C_{12}H_{12}O_5$: C, 61·0; H, 5·2%). Mixed m. p.s with 2 : 5-dihydroxyacetophenone and its diacetate respectively showed no depression.

Condensation of quinol with dibenzoyloxymaleic anhydride in the same way provided 2 : 5-dihydroxybenzophenone (39%), m. p. and mixed m. p. 123°.

Persulphate Oxidation of 3-*Hydroxyjuglone.*—To a stirred solution of 3-hydroxyjuglone (1·9 g.) in 10% aqueous sodium hydroxide (20 c.c.) was added during 4 hr. saturated aqueous potassium persulphate (2·7 g.) so that the temperature did not exceed 20°. Next day the solution was acidified (Congo-red) with dilute sulphuric acid, and starting material recovered by filtration and ether-extraction. Concentrated hydrochloric acid (50 c.c.) was then added, and the mixture heated on the steam-bath for 30 min. and then repeatedly extracted with ether. Evaporation of the solvent left a red solid (0·1 g.) which was acetylated by warm acetic anhydride and a trace of concentrated sulphuric acid. Repeated crystallisation from alcohol afforded yellow needles of *triacetate*, m. p. 142° (Found : C, 56·8; H, 3·9. $C_{16}H_{12}O_8$ requires C, 57·8; H, 3·65%).

Persulphate Oxidation of 1-*Hydroxyanthraquinone.*—A solution of 1-hydroxyanthraquinone (15 g.) in 10% sodium hydroxide solution (134 c.c.) and pyridine (10 c.c.) was treated with potassium persulphate (18 g.) as before. Starting material was recovered by acidification and filtration, and the filtrate was then heated on the steam-bath for 1 hr. after the addition of more hydrochloric acid. Quinizarin was isolated by repeated extraction with ether and after crystallisation from alcohol had m. p. and mixed m. p. 195° (50 mg.). The diacetate had m. p. 208°.

1 : 2 : 3 : 4-*Tetrahydro*-7 : 8-*dimethoxy*-1-*oxonaphthalene.*—A solution of 5-chloro-1 : 2 : 3 : 4-tetrahydro-7 : 8-dimethoxy-1-oxonaphthalene (0·5 g.) (Ghosh and Robinson, *J.*, 1944, 507) in alcohol (100 c.c.) was shaken with hydrogen, 2% palladised strontium carbonate (1·5 g.), and ethanolic 10% potassium hydroxide (10 c.c.) until 48 c.c. of hydrogen had been absorbed. After filtration and evaporation to dryness, the residue was stirred with water and extracted with ether and dried (K_2CO_3). After removal of the solvent the residue was distilled at 0·001 mm. The fraction of b. p. 110° (bath) crystallised. This *ketone* recrystallised from light petroleum (b. p. 40°) in clusters of needles, m. p. 57·5° (0·35 g.) (Found : C, 69·35; H, 6·65. $C_{12}H_{14}O_3$ requires C, 69·85; H, 6·8%). The 2 : 4-*dinitrophenylhydrazone* formed fine orange needles, m. p. 180° (from alcohol) (Found : C, 55·75; H, 4·7; N, 14·4. $C_{18}H_{18}O_6N_4$ requires C, 55·95; H, 4·7; N, 14·5%).

3-*Hydroxy*-5 : 6-*dimethoxy*-1 : 4-*naphthaquinone.*—Aqueous 10% sodium hydroxide (5 c.c.) was added to a solution of the above ketone (2·8 g.) and *p*-nitrosodimethylaniline (5 g.) in alcohol (200 c.c.), and the mixture set aside for 18 hr. The purple crystals of the dianil which had separated were collected, dried (1·3 g.), and dissolved in water (100 c.c.) containing concentrated sulphuric acid (5 c.c.). The blood-red solution became orange and formed a brown precipitate after being boiled for 1¼ hr. The solid was collected on cooling and a further quantity obtained by chloroform extraction of the filtrate. The *quinone* crystallised from light petroleum (b. p. 100—120°) in yellow needles, m. p. 205—206° (decomp.) (0·5 g.) (Found : C, 61·3; H, 4·25. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%).

3 : 5 : 6-*Triacetoxy*-1 : 4-*naphthaquinone.*—3-Hydroxy-5 : 6-dimethoxy-1 : 4-naphthaquinone (0·3 g.) was added with stirring to a fused mixture of sodium chloride (2·4 g.) and anhydrous aluminium chloride (12 g.) at 110°. The temperature was raised to 180° for 1 min., the mixture cooled, and the solid dissolved in dilute hydrochloric acid. The solution was raised to the boil, then cooled and the precipitate thus obtained was collected. The crude product was difficult to purify. It was obtained as brick-red microcrystals, decomp. 225—230°, after crystallisation from benzene followed by sublimation *in vacuo* and converted into the *triacetate* which formed yellow needles, m. p. 150—151° (from alcohol) (Found : C, 57·7; H, 3·6. $C_{16}H_{12}O_8$ requires C, 57·85; H, 3·65%).

Naphthazarin Dimethyl Ether (cf. Brass, Pfluger, and Honsberg, *Ber.*, **1936**, **69**, 87).—A mixture of naphthazarin (2 g.), sodium carbonate (5·6 g.; dried at 150°), methyl toluene-*p*-sulphonate (8 g.), and *o*-dichlorobenzene (25 c.c.) was refluxed for 2 hr. Water which appeared in the condenser was removed. The cooled solution was filtered and the filtrate diluted with light petroleum (b. p. 100—120°; 150 c.c.). An orange-brown solid separated and more was

obtained by removing the solvent under reduced pressure. The crude product was sublimed *in vacuo* and then crystallised from light petroleum (b. p. 100—120°) forming orange needles, m. p. 157° (44%).

Addition Reactions.—With chlorine. (*a*) Excess of dry chlorine was passed into a suspension of naphthazarin (1 g.) in glacial acetic acid (100 c.c.), and the mixture left in a stoppered flask exposed to sunlight for 3 days by which time all the quinone had dissolved, the colour changing from wine-red to reddish-yellow. The solution was then poured on ice, forming a yellow precipitate; this was dissolved in glacial acetic acid (50 c.c.) along with anhydrous sodium acetate (3 g.), and the mixture was boiled for 5 min. On cooling, the red solution was diluted with water, and the precipitated chloronaphthazarin collected and crystallised from alcohol, forming needles with a green metallic sheen, m. p. 179° (76%). The diacetate had m. p. 194°. (*b*) Excess of dry chlorine was added to a suspension of naphthazarin diacetate (1 g.) in glacial acetic acid (50 c.c.), and the mixture left in a stoppered flask exposed to sunlight for 2 days. The resulting solution was then worked up as in (*a*). Chloronaphthazarin diacetate crystallised from alcohol in yellow needles, m. p. 194° (75·5%), identical with those obtained as in (*a*). (*c*) Dry chlorine (10% excess) was passed into a solution of naphthazarin dimethyl ether (1 g.) in glacial acetic acid (40 c.c.). The initially dark brown solution rapidly became yellow. The mixture was then treated as in (*a*). *2-Chloronaphthazarin dimethyl ether* crystallised from alcohol in scarlet plates, m. p. 201° (90%) (Found: C, 56·9; H, 3·5; Cl, 13·9. $C_{12}H_9O_4Cl$ requires C, 57·0; H, 3·6; Cl, 14·0%). Demethylation with sodium chloride–aluminium chloride gave chloronaphthazarin. The dimethyl ether was also obtained as follows: a mixture of chloronaphthazarin (0·35 g.), anhydrous sodium carbonate (0·4 g.), methyl toluene-*p*-sulphonate (0·8 g.), and *o*-dichlorobenzene (8 c.c.) was refluxed until the original red solution had changed to yellow (*ca.* 1 hr.). Water which separated was removed at intervals. When cool, the mixture was filtered and the filtrate diluted with light petroleum (b. p. 100—120°; 25 c.c.). The precipitate thus obtained was sublimed at 100°/0·001 mm. Crystallisation of the orange sublimate from alcohol afforded a mixture (9 : 1) of brown-yellow needles and reddish plates. The latter were separated by hand-picking and had m. p. 196° not depressed by the product obtained as in (*c*).

*With toluene-*p*-thiol.* (*a*) To a solution of naphthazarin (0·45 g.) in alcohol (50 c.c.) was added toluene-*p*-thiol (0·15 g.) in alcohol (10 c.c.). The mixture was boiled under reflux for 5 min., set aside overnight, then concentrated to 20 c.c. The dark red solid which separated was crystallised first from light petroleum (b. p. 100—120°) and then (a little red oil being discarded) from alcohol. The *tolylthioquinone* formed fine ruby needles with a slight green sheen, m. p. 156° (40·5%) (Found: S, 10·4. $C_{17}H_{12}O_4S$ requires S, 10·2%). (*b*) To a solution of naphthazarin (0·3 g.) in alcohol (50 c.c.) was added toluene-*p*-thiol (2 g.). The mixture was boiled under reflux for 5 min. and left overnight. A microcrystalline deposit was collected and crystallised from light petroleum (b. p. 100—120°). The *ditolylthioquinone* separated in dark red needles with a green sheen, m. p. 230° (44%) (Found: S, 14·4. $C_{24}H_{18}O_4S_2$ requires S, 14·7%). (*c*) To a solution of naphthazarin diacetate (0·4 g.) in alcohol (40 c.c.) was added a solution of toluene-*p*-thiol (0·15 g.) in alcohol (10 c.c.). The mixture was boiled under reflux for 5 min., and, next morning, concentrated to 20 c.c. The *product*, which separated on cooling, formed yellow plates, m. p. 184° (from alcohol) (26%) (Found: C, 63·6; H, 4·1; S, 8·9. $C_{21}H_{16}O_6S$ requires C, 63·8; H, 4·1; S, 8·1%). (*d*) To a solution of naphthazarin dimethyl ether (0·8 g.) in alcohol (6 c.c.) was added a solution of toluene-*p*-thiol (0·25 g.) in alcohol (6 c.c.). After boiling under reflux for 5 min. the mixture was allowed to cool overnight. The *product* which separated was recrystallised first from alcohol and then from benzene–light petroleum forming red-brown needles, m. p. 163·5° (32%) (Found: C, 66·8; H, 5·0; S, 8·8. $C_{19}H_{16}O_4S$ requires C, 67·0; H, 4·75; S, 9·4%).

With aniline. (*a*) (cf. Fierz-David and Stockar, *loc. cit.*) Naphthazarin (1 g.) was stirred with aniline (25 c.c.) for 24 hr. The mixture was then diluted with alcohol, and the fine crystalline precipitate washed with alcohol and crystallised from *o*-dichlorobenzene in dark green plates, m. p. 233° (61%). (*b*) A mixture of naphthazarin diacetate (0·4 g.), alcohol (40 c.c.), and aniline (0·1 g.) was boiled for 5 min., allowed to cool overnight, and then concentrated to half bulk. Unchanged starting material separated. (*c*) Naphthazarin diacetate (1 g.) was stirred with aniline (25 c.c.) for 24 hr. The mixture was then stirred with dilute hydrochloric acid, and the precipitate obtained crystallised from alcohol to give unchanged starting material. (*d*) A solution of naphthazarin dimethyl ether (0·8 g.) in alcohol (6 c.c.) containing aniline (0·2 g.) was boiled for a few minutes and left to cool. On removal of the solvent *in vacuo* and sublimation of the residue *in vacuo* unchanged naphthazarin dimethyl ether was obtained as the sole

product. (*e*) A suspension of naphthazarin dimethyl ether (1 g.) in aniline (25 c.c.) was stirred for 3 days. All the starting material was recovered.

2-Hydroxynaphthazarin Dimethyl Ether.—To a solution of naphthazarin dimethyl ether (0·5 g.) in alcohol (20 c.c.) was added a solution of sodium carbonate (0·5 g.) in water (5 c.c.) together with hydrogen peroxide (1 c.c.; 100-vol.). The original orange solution became straw-coloured and after several hours a yellow precipitate was collected and crystallised from light petroleum (b. p. 100—120°). The *hydroxyquinone* formed yellow needles, m. p. 194° (0·4 g.) (Found: C, 61·35; H, 4·3. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%). The quinone gave a dark yellow solution in aqueous sodium hydroxide and an orange solution in concentrated hydrochloric acid. Demethylation yielded naphthopurpurin.

2-Chloro-3-methylnaphthazarin.—A solution of dry chlorine (0·5 g.) in glacial acetic acid (10 c.c.) was added to a suspension of methylnaphthazarin diacetate (1 g.) in glacial acetic acid (20 c.c.) and the mixture exposed to sunlight for 2 days, by which time all the quinone had dissolved. The solution was then poured on ice, and the precipitated solid was collected, dissolved in glacial acetic acid (10 c.c.), and boiled for 5 min. with excess of sodium acetate. On cooling and dilution with water *2-chloro-3-methylnaphthazarin diacetate* separated. It crystallised from light petroleum (b. p. 100—120°) in yellow needles, m. p. 186° (0·9 g.) (Found: C, 55·6; H, 3·6; Cl, 9·9. $C_{15}H_{11}O_6Cl$ requires C, 55·85; H, 3·45; Cl, 11·0%). The diacetate (0·25 g.) was refluxed with 5N-hydrochloric acid (100 c.c.) until all dissolved and a red precipitate had appeared. This was collected after cooling and crystallised from alcohol. *2-Chloro-3-methylnaphthazarin* separated as red needles with a green metallic sheen, m. p. 189° (0·18 g.) (Found: C, 55·3; H, 3·0; Cl, 14·95. $C_{11}H_7O_4Cl$ requires C, 55·4; H, 2·95; Cl, 14·85%).

Toluene-p-sulphonylnaphthazarin.—A mixture of naphthazarin (1 g.), sodium *p*-toluenesulphinate (2·5 g.), acetone (100 c.c.), water (10 c.c.), and 2N-hydrochloric acid (10 c.c.) was shaken for 10 min. and set aside for 1 hr. with occasional shaking. The solution was filtered and oxidised by the addition of potassium dichromate (4 g.) in water (100 c.c.) containing concentrated sulphuric acid (4 c.c.). Next morning the purple *product* precipitated (0·45 g.) was collected and crystallised from benzene–light petroleum, forming dark red micro-needles, m. p. 271° (Found: C, 59·0; H, 3·6; S, 9·5. $C_{17}H_{12}O_6S$ requires C, 59·3; H, 3·5; S, 9·3%).

Dipotassium 1 : 2 : 3 : 4-Tetrahydro-1 : 4-dioxonaphthalene-(2 : 6 ?)-disulphonate.—Finely divided naphthazarin (2 g.) was added gradually to a stirred solution of potassium metabisulphite (2·6 g.) in water (15 c.c.) in 20 min. Methyl alcohol (5—10 c.c.) was then added and the mixture stirred overnight, the quinone dissolving gradually and a product then being precipitated. Saturated aqueous potassium chloride (15 c.c.) was added, stirring continued for several hours, and the precipitate then collected, dried, stirred with cold chloroform (twice), and dried (2·25 g.). This material was extracted several times with boiling alcohol and dried *in vacuo* as a yellow microcrystalline powder (Found: C, 27·7; H, 1·7; S, 14·95. $C_{10}H_6O_{10}K_2S_2$ requires C, 28·0; H, 1·4; S, 14·95%). The *sulphonate* formed a pale yellow solution in water, which on addition of sodium hydroxide rapidly changed through orange, brown, and green to blue. The salt gave a red solution in hot dilute acid and a bright yellow one when heated in acid stannous chloride solution. No coloured material was extracted from acid solutions with chloroform. Material prepared by the Colour Index recipe was similar.

Reduction of Naphthazarins with Acid Stannous Chloride.—By the procedure described before (Bruce and Thomson, *loc. cit.*), 2 : 3- and 2 : 6-dichloro-, *p*-tolylthio-, di-*p*-tolylthio-, and toluene-*p*-sulphonyl-naphthazarin all gave 1 : 2 : 3 : 4-tetrahydro-5 : 8-dihydroxy-1 : 4-dioxonaphthalene. The mixture of 6- and 7-chloro-2-methylnaphthazarin gave 1 : 2 : 3 : 4-tetrahydro-5 : 8-dihydroxy-6-methyl-1 : 4-dioxonaphthalene. 2-Chloro-3-methylnaphthazarin afforded *6-chloro-1 : 2 : 3 : 4-tetrahydro-5 : 8-dihydroxy-7-methyl-1 : 4-dioxonaphthalene* in yellow needles, m. p. 185° (from methanol) (Found: C, 55·2; H, 3·65. $C_{11}H_9O_4Cl$ requires C, 54·9; H, 3·8%). 2 : 6-Dimethylnaphthazarin yielded *1 : 2 : 3 : 4-tetrahydro-5 : 8-dihydroxy-2 : 6-dimethyl-1 : 4-dioxonaphthalene* which sublimed at 130°/0·001 mm. in orange needles, m. p. 150° (Found: C, 65·70; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·45; H, 5·5%).

[*HO*-$^2H_5$]Naphthazarin was obtained by hydrolysis of naphthazarin diacetate with a dilute solution of deuterium sulphate in deuterium oxide and purified by sublimation *in vacuo*.

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Anodic Syntheses. Part XIII. Chain Extension of Fatty Acids by Electrolysis with Benzyl Half Esters.*

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Chain extension of fatty acids by electrolysis with benzyl hydrogen succinate gives products of high purity. Evidence is presented for the *cis*-configuration of natural eicos-11-enoic acid.

Many fatty acids are conveniently synthesised by anodic crossed coupling of a monocarboxylic acid with a half ester of a dicarboxylic acid (cf. previous papers in this series) :

$$R{\cdot}CO_2H + \underset{(I)}{HO_2C{\cdot}[CH_2]_n{\cdot}CO_2R'} \longrightarrow R{\cdot}[CH_2]_n{\cdot}CO_2R' \longrightarrow R{\cdot}[CH_2]_n{\cdot}CO_2H$$

If the starting materials are suitably chosen, the product is free from substances of similar molecular weight, and is therefore readily purified.

Recently it has been observed that during the electrolysis of a fatty acid, some esterification with the methanol used as solvent may accompany the coupling processes. It has long been known that acids in which the carboxyl group is directly attached to an aromatic or alicylic ring do not couple to any appreciable extent. A number of such substances have been shown to undergo some esterification at the anode (Fichter and Meyer, *Helv. Chim. Acta*, 1934, **17**, 541; Fichter and Simon, *ibid.*, p. 1218; Fichter and Holbro, *ibid.*, 1938, **21**, 141; Fichter and Stenzl, *ibid.*, 1939, **22**, 971). These reactions are probably related to the formation of esters $R{\cdot}CO_2R$, by a process of the Hofer–Moest type, during the electrolysis of acids $R{\cdot}CO_2H$ in aqueous media (Kolbe, *Annalen*, 1849, **69**, 257; Petersen, *Z. physikal. Chem.*, 1900, **33**, 116; cf. Weedon, *Quart. Rev.*, 1952, **6**, 380). In small-scale preparations involving the anodic chain extension of a fatty acid by only a few carbon atoms, the side reaction with the solvent may result in contamination of the product with the starting material (cf. Part XII). Of the methods so far tried for avoiding this drawback, the use of the benzyl half ester (I; $R' = CH_2Ph$) in place of the methyl or ethyl half ester has shown most promise. The benzyl ester then formed by crossed coupling with the monocarboxylic acid may be either separated by distillation from any methyl ester of the starting material and subsequently hydrolysed, or, alternatively, converted without isolation into the required acid by hydrogenolysis. Three examples of two-carbon homologation are given in this paper to illustrate these procedures. Three recent communications have described the use of benzyl esters in the anodic synthesis of dicarboxylic acids (Dolejš and Novotný, *Coll. Czech. Chem. Comm.*, 1954, **19**, 716; Šorm, Streibl, Jarolím, Novotný, Dolejš, and Herout, *Chem. Listy*, 1954, **48**, 575; cf. *Chem. and Ind.*, 1954, 252).

Electrolysis in methanol of myristic (n-C_{14}) acid with 3 mols. of benzyl hydrogen succinate, and alkaline hydrolysis of the benzyl esters formed, gave palmitic (n-C_{16}) acid in 30% yield. When stearic (n-C_{18}) and *threo*-9 : 10-dihydroxystearic acid were similarly electrolysed with benzyl hydrogen succinate (2·5—3 mols.), and the resulting esters hydrogenolysed, arachidic (n-C_{20}) and 11 : 12-dihydroxyarachidic acid were obtained in 25 and 13% yield respectively. No difficulty was encountered in the purification of these three products, only a single crystallisation of each of the "crude" materials being required. The expected products of symmetrical coupling were also formed : when benzyl hydrogen succinate was electrolysed alone in methanol, benzyl adipate was obtained in 50% yield.

Since *vic.*-dihydroxy-acids are readily derived from, and converted into, the corresponding ethylenic acids (cf. Bounds, Linstead, and Weedon, *J.*, 1953, 2393), the method used to synthesis 11 : 12-dihydroxyarachidic acid can obviously be extended to the preparation of unsaturated fatty acids.

* Part XII, *J.*, 1954, 4219.

Another feature of the dihydroxyarachidic acid synthesis described above also deserves mention: it provides the first proof that natural eicos-11-enoic acid has the *cis*-configuration. This had previously been assumed by analogy with oleic acid (Hopkins, Chisholm, and Harris, *Canad. J. Res.*, 1949, **27**, 35). Eicos-11-enoic acid is the chief component acid of jojoba oil, the unique liquid seed wax of *Simmondsia californica* (Green, Hilditch, and Stainsby, *J.*, 1936, 1750; Eckey, "Vegetable Fats and Oils," Reinhold Publ. Corp., New York, 1954), and is a constituent of the glycerides in Atlantic cod liver oil, *Gadus callarias* (Hopkins *et al.*, *loc. cit.*) (for references to other minor sources, see *idem*, *loc. cit.*; Tsuchiya, *J. Chem. Soc. Japan*, 1951, **54**, 672; Hatt and Szumer, *J. Soc. Food Agric.*, 1953, **4**, 273). By stereospecific oxidations, the natural acid has been converted into both possible racemates of 11 : 12-dihydroxyarachidic acid (Green *et al.*, Hopkins *et al.*, Hatt and Szumer, *locc. cit.*; Baliga and Hilditch, *J.*, 1949, S 91); the properties reported for the low-melting form, obtained by oxidation with either peracetic or performic acid (*trans*-addition), are in good agreement with those of the anodic product. This, like the starting material which was prepared by performic acid oxidation of (*cis*-)oleic acid, must have the *threo*-structure, because the 9 : 10-dihydroxystearic acids are known to couple anodically with complete retention of configuration (Bounds, Linstead, and Weedon, *loc. cit.*). A stereochemical correlation between oleic and (natural) eicos-11-enoic acid has now, therefore, been established. No such connection was furnished by the partial syntheses of eicos-11-enoic acid from oleic acid (Vesely and Chudožilov, *Coll. Czech. Chem. Comm.*, 1930, **2**, 95; Fieser and Chamberlin, *J. Amer. Chem. Soc.*, 1948, **70**, 71), as the malonate method of chain extension used leads to extensive stereomutation (cf. Bounds, Linstead, and Weedon, *J.*, 1954, 448; Part XII).

Experimental

M. p.s were determined on samples in capillary tubes, and are uncorrected. In those experiments for which a recovery of starting material is given, allowance for this has been made in calculating the yields of the products. Conditions for the hydrolysis and hydrogenolysis of long-chain benzyl esters were established by pilot experiments on an authentic specimen of benzyl palmitate (Shonle and Row, *J. Amer. Chem. Soc.*, 1921, **43**, 361). The palladium catalysts used in the hydrogenolyses were prepared as described by Bowman (*J.*, 1950, 327).

Electrolyses.—These were carried out in cell "B" (Part IX, *J.*, 1953, 2393). The solvent used was commercial absolute methanol, to which sufficient sodium had been added to neutralise *ca.* 2% of the total acids. During the experiments the cell was cooled in an ice-bath (internal temp. of cell $<50°$), and the direction of the current was reversed from time to time. Electrolyses were continued until the electrolyte became slightly alkaline; this required *ca.* 3 times the number of Faradays calculated on the basis of the current and the amounts of acids used.

Benzyl Hydrogen Succinate (cf. Howard, *J. Amer. Chem. Soc.*, 1922, **44**, 1763).—A mixture of succinic anhydride (30 g.) and benzyl alcohol (33 g.) was heated under reflux for 4 hr. and then cooled. The product was extracted thoroughly with ether, and the ethereal solution was separated from the insoluble residue of succinic acid and washed repeatedly with saturated sodium carbonate solution. The alkaline extracts were acidified with 2N-hydrochloric acid, and the product (30 g., 48%), m. p. 58—59°, thus precipitated was isolated in the usual way with ether. Crystallisation from benzene–light petroleum (b. p. 80—100°) gave the half ester, m. p. 60° (Found: C, 63·7; H, 6·0. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·8%) (*idem*, *loc. cit.*, gives m. p. 55—56°).

Benzyl Adipate.—A solution of benzyl hydrogen succinate (5 g.) in methanol (12·5 c.c.) was electrolysed (0·5 amp.). The cell contents were filtered, acidified with glacial acetic acid, and evaporated under reduced pressure. The residue was extracted with benzene (500 c.c.), and the solution was washed with saturated sodium carbonate, dried, and evaporated. Distillation of the residue gave a liquid (0·5 g.), b. p. 65—70°/0·2 mm., and benzyl adipate (2·0 g.), b. p. 170—175°/0·25 mm., which crystallised from light petroleum (b. p. 40—60°) and had m. p. 38·5—39·5°, undepressed on admixture with a specimen prepared from sodium adipate and benzyl chloride (Found: C, 73·8; H, 6·9. Calc. for $C_{20}H_{22}O_4$: C, 73·6; H, 6·8%) (Millat, *Ann. pharm. franç.*, 1949, **7**, 105, gives m. p. 39°). Alkaline hydrolysis gave adipic acid, m. p. and mixed m. p. 149—150°.

Palmitic Acid.—(a) *Hydrolysis of benzyl palmitate.* Benzyl palmitate (0·5 g.) was added to sodium hydroxide (0·5 g.) in methanol (2 c.c.) and water (0·5 c.c.), and the mixture was heated under reflux for 3 hr. Water was added, the methanol was distilled off, and the aqueous solution was boiled with excess of 30% hydrochloric acid. After the mixture had been cooled, the product was isolated with ether and crystallised from methanol, giving palmitic acid (0·35 g., 95%), m. p. and mixed m. p. 60—62°.

(b) *Hydrogenolysis of benzyl palmitate.* A solution of benzyl palmitate (0·7 g.) in ethyl acetate (50 c.c.) was shaken in an atmosphere of hydrogen, first with 10% palladised charcoal (0·2 g.) overnight, and then with 10% palladised strontium carbonate (0·3 g.) for 4 hr. Removal of catalyst and solvent, and crystallisation of the residue from methanol, gave palmitic acid (0·45 g., 87%), m. p. and mixed m. p. 60—62°.

(c) *Anodic synthesis from myristic acid.* A solution of myristic acid (5·5 g.; m. p. 54°) and benzyl hydrogen succinate (15 g., 3 mols.) in methanol (70 c.c.) was electrolysed (1·0 amp.). The cell contents were filtered, acidified with glacial acetic acid, and evaporated. The residue was extracted with benzene (500 c.c.), and the solution was washed thoroughly with 2N-potassium hydroxide. On acidification of the alkaline extract myristic acid (0·6 g.), m. p. and mixed m. p. 54—55°, was recovered. The benzene layer was washed with water, dried ($CaCl_2$), and evaporated. Distillation of the residue gave three fractions: (i) A liquid (1·8 g.), b. p. 70—90°/0·3 mm. (ii) A fraction (1·0 g.), b. p. 150—175°/0·6 mm., which partly solidified. (iii) A fraction (8·1 g.), b. p. 175—210°/0·6 mm., which partly solidified. Fraction (iii) and sodium hydroxide (8·1 g.) in water (8·1 c.c.) and methanol (32·4 c.c.) were boiled under reflux for 4 hr. The excess of alkali was then neutralised by 2N-hydrochloric acid, and the resulting mixture was evaporated to dryness. The residue was extracted (Soxhlet) with benzene for 24 hr. Evaporation of the benzene solution, and crystallisation of the product from light petroleum (b. p. 40—60°), gave hexacosane (0·9 g., 23%), m. p. and mixed m. p. 55—56°. Treatment of the benzene-insoluble material with hot hydrochloric acid yielded a solid, m. p. 60—61°. One crystallisation from methanol gave palmitic acid (1·7 g., 30%), m. p. and mixed m. p. 62—63° (Found: C, 74·85; H, 12·7%; equiv., 261. Calc. for $C_{16}H_{32}O_2$: C, 74·95; H, 12·6%; equiv., 256). On concentration of the mother-liquors from the acidification, adipic acid (1·0 g., 19%), m. p. and mixed m. p. 149—150°, was obtained.

Arachidic Acid.—A solution of stearic acid (5·9 g.; m. p. 68·5°) and benzyl hydrogen succinate (13 g.; 2·5 mols.) in methanol (80 c.c.) was electrolysed (1·3 amp.). Isolation of the products as in the preceding experiment yielded stearic acid (1·5 g.), m. p. and mixed m. p. 68—68·5°, and a neutral fraction. Distillation of the latter gave a liquid (2 g.), b. p. 80—120°/0·2 mm., and a liquid (7·8 g.), b. p. 180—265°/0·25 mm., which partly solidified. A solution of the high-boiling fraction in ethyl acetate (500 c.c.) was cooled to 0°, and the solid which separated was collected. Crystallisation from ether giving tetratriacontane (1·0 g., 27%), m. p. 73—74° (Found: C, 85·3; H, 14·85. Calc. for $C_{34}H_{70}$: C, 85·25; H, 14·7%) (Petersen, *Z. Electrochem.*, 1906, **12**, 144, gives m. p. 72·9°).

The ethyl acetate solution was shaken in hydrogen, first with 10% palladised charcoal (2 g.) overnight, and then with 10% palladised strontium carbonate (2 g.) for 7 hr. The catalyst and solvent were removed, and the residue was extracted with benzene. Separation of the insoluble material gave adipic acid (1·3 g., 29%), m. p. and mixed m. p. 149—150°. The benzene solution was washed thoroughly with 2N-potassium hydroxide, and the extract was boiled with excess of 30% hydrochloric acid. Isolation of the product with ether gave a solid, m. p. 73°. One crystallisation from alcohol furnished arachidic acid (1·2 g., 25%), m. p. 74·5—75·5° (remelt 75—75·5°) unchanged by further crystallisation (Found: C, 76·9; H, 13·05%; equiv., 308·5. Calc. for $C_{20}H_{40}O_2$: C, 76·85; H, 12·9%; equiv., 312). Francis and Piper (*J. Amer. Chem. Soc.*, 1939, **61**, 577) give m. p. 75·35°.

threo-11 : 12-*Dihydroxyarachidic Acid.*—A solution of *threo*-9 : 10-dihydroxystearic acid (4·6 g.; m. p. 93°) and benzyl hydrogen succinate (9·2 g.; 3 mols.) in methanol (60 c.c.) was electrolysed (1·2 amp.). The solid which separated during the electrolysis was filtered off, giving tetratriaconta-*threo*-9 : 10-*threo*-25 : 26-tetraol (1·2 g.; 30%), m. p. and mixed m. p. 123° (Bounds, Linstead, and Weedon, *J.*, 1953, 2393, give m. p. 124—124·5°). The filtrate was neutralised with glacial acetic acid and evaporated. The residue was extracted with benzene (500 c.c.), and the solution was washed with N-potassium hydroxide and water. Acidification of the alkaline extract gave *threo*-9 : 10-dihydroxystearic acid (0·1 g.), m. p. and mixed m. p. 92—93°. Evaporation of the benzene solution gave a liquid (7·4 g.) which was hydrogenolysed in ethyl acetate (500 c.c.) in the usual way. Isolation of the products as in the preceding experiment gave adipic acid (0·7 g., 22%), m. p. and mixed m. p. 149—150°, and a solid, m. p.

94°. One crystallisation of the latter from benzene gave *threo*-11 : 12-dihydroxyarachidic acid (0·6 g., 13%), m. p. 95—96° (Found : C, 69·9; H, 11·8%; equiv., 345. Calc. for $C_{20}H_{40}O_4$: C, 69·7; H, 11·7%; equiv., 344·5). Hopkins, Chisholm, and Harris (*Canad. J. Res.*, 1949, **27**, 35) give m. p. 95—96° for the dihydroxy-acid prepared by peracetic acid oxidation of natural eicos-11-enoic acid.

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Cellular Constituents. The Chemistry of Xanthine Oxidase. Part I. The Preparation of a Crystalline Xanthine Oxidase from Cow's Milk.

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[Reprint Order No. 5711.]

A procedure for the preparation of a crystalline metallo-flavoprotein from buttermilk is described. It possesses high xanthine oxidase activity (Q_{O_2} = 2300; spectrophotometric assay with xanthine at 23·5°) and a protein/flavin ratio (*i.e.*, E_{280}/E_{450}) of 5·0—5·2, the lowest reported for material with such enzymic properties.

Xanthine oxidase controls biologically the last stages of nucleic acid catabolism by removal of hypoxanthine and xanthine in the form of uric acid from the general pool of purines. Its presence in excess or its absence, its inhibition or stimulation, might possibly reflect on the chemistry of normal or abnormal cellular growth. When examining such a hypothesis Haddow *et al.* (*Brit. Emp. Cancer Camp. Ann. Report*, 1953, **31**, 35) found, first, that xanthopterin and some related compounds which induce hypertrophy of the kidney in rodents inhibit bovine xanthine oxidase *in vitro* and, secondly, that injections of xanthine oxidase concentrates from cow's milk into mice bearing spontaneous mammary tumours produce, apparently, antitumour effects. Although exceptions to the hypertrophy-inhibition correlation have been encountered and the preliminary results in the mouse need further confirmation, we were encouraged to embark on a thorough study of the chemistry of this enzyme.

The preparation of highly active material from cow's milk has been achieved in a number of laboratories, *e.g.*, by Corran, Dewan, Gordon, and Green (*Biochem. J.*, 1939, **33**, 1694), Ball (*J. Biol. Chem.*, 1939, **128**, 51), Horecker and Heppel (*ibid.*, 1949, **178**, 683), Morell (*Biochem. J.*, 1952, **51**, 657), and Mackler, Mahler, and Green (*J. Biol. Chem.*, 1954, **210**, 149). Their products were not crystalline and none of the authors claimed a homogeneous product. The identity, or otherwise, of the bovine milk enzyme with the xanthine oxidases of animal and human somatic tissues has not so far been ascertained.

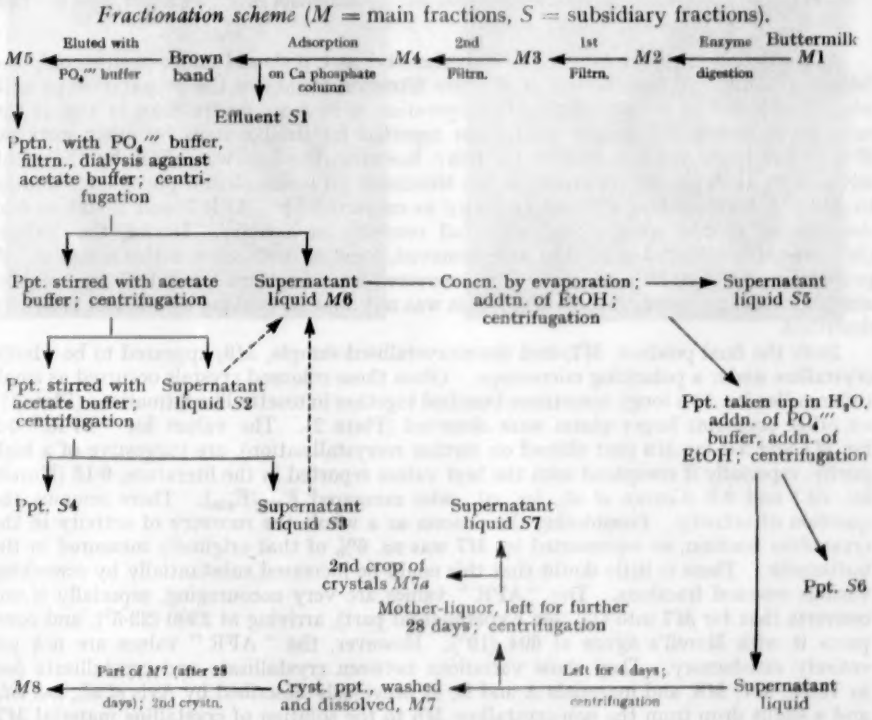
Using improved preparative methods we have obtained from buttermilk an active crystalline metallo-flavoprotein as reported in a preliminary communication (Avis, Bergel, Bray, and Shooter, *Nature*, 1954, **173**, 1230). In the present paper we describe our preparative procedures in detail and give the relevant assay figures.

The progressive purification of the enzyme was followed by means of the following measurements : optical densities at 280 mμ (" protein ") and 450 mμ (" flavin ") (cf. Corran *et al.*, *loc. cit.*), and the slope $\Delta E_{295\ m\mu}/\Delta t_{(min.)}$ in the presence of xanthine (" enzyme activity ") (Kalckar, *J. Biol. Chem.*, 1947, **167**, 429; Morell, *loc. cit.*). Details of these assay methods and definitions of the unit of activity are given in the Experimental section, where also evidence can be found that solutions of the enzyme, unlike certain other proteins (cf. Champagne, *J. Chim. phys.*, 1950, **47**, 693; Rosenberg *et al.*, *Bull. Soc. Chim. biol.*,

1953, **35**, 521), obey Beer's law over the range of concentrations employed. From the three sets of figures obtained, the ratios Activity (units/l.)/E_{280} = " APR," E_{280}/E_{450} = " PFR," and Activity (units/l.)/E_{450} = " AFR " were calculated for each fraction. These ratios give a fair picture of the composition of any fraction containing xanthine oxidase. " APR " is directly proportional to activity per unit weight of protein and therefore to the conventional Q_{O_2} (cf. Morell, *loc. cit.*) if variations in the absorption coefficient ($E^{1\%}_{1\,cm.}$) of different proteins at 280 mμ are ignored and if this assumption is accepted as coming nearer the truth with increasing purity of the preparations. " PFR " depends largely on the relative amounts of coloured material and total protein; thus once xanthine oxidase forms the only constituent of the preparation absorbing at 450 mμ, a decrease in " PFR " must represent a higher purity. The third ratio " AFR " has been little used by other workers except that Corran *et al.* (*loc. cit.*) reported that their Activity/" apparent flavin phosphate " ratio for most but not all preparations remained constant from an early stage in their purification. In our case we have taken an increase of " AFR " as an indication of the removal of inactive coloured impurities, while a decrease during the later stages of purification was considered as a sign of increase in the proportion of inactive to active enzyme (cf. Morell, *loc. cit.*).

From the annexed scheme, it can be seen that the main steps of our procedure are these: production of whey from buttermilk by removal of casein through the action of

Fractionation scheme (*M* = main fractions, *S* = subsidiary fractions).



pancreatin (cf. Ball, *loc. cit.*), followed by pressure filtration; chromatographic adsorption on a calcium phosphate column (cf. Polis and Shmukler, *J. Biol. Chem.*, 1953, **201**, 475, with peroxidase), and elution with phosphate buffer (cf. Horecker and Heppel, *loc. cit.*); precipitation of impurities at low salt concentrations (acetate buffer), and fractionation and crystallisation in presence of ethanol and very dilute phosphate buffer. This scheme has

been followed with a considerable number of batches, all giving generally the same results. The assay figures of all fractions of a typical batch are given in the Table.

Fraction	Volume (l.)	Total Units X.O.	"AFR"	"APR"	"PFR"	Remarks
*M*1	25	277	—	0·14 *	—	Buttermilk
*M*2	25	275	—	—	—	After pancreatin treatment
*M*3	21	96	—	—	—	1st filtrate
*M*4	20	85	35	0·53	65	2nd filtrate (whey)
*M*5	1·22	96 †	70	7·4	9·4	Eluate
*M*6	0·45	43	88	11·1	8·0	"Starting concentrate"
*M*7	0·050	17	79	15·2	5·2	Crystalline
*M*7*a*	0·015	3	66	10·4	6·3	"
*M*8	—	—	71 ‡	14·2 ‡	5·0 ‡	"
*S*1	20	0·2	0·2	0·001	170	Effluent, see *M*5
*S*2	0·16	10	99	12·5	7·9	Supernatant, see *M*6
*S*3	0·13	3	83	12·2	6·9	Supernatant, see *M*6
*S*4	0·15	20	37 *	4·2 *	8·8 *	Precipitate, see *S*3
*S*5	0·32	4	73	6·8	10·7	Supernatant
*S*6	0·022	6	81	6·2	13·1	Precipitate
*S*7	0·095	1·7	63	4·6	13·7	Supernatant, see *M*7 and *M*7*a*
A	—	—	32	6·1	5·3	Crystalline (cf. Avis *et al.*, *loc. cit.*)
B	—	—	53	10·4	5·1	Crystalline (cf. Avis *et al.*, *loc. cit.*)

* Value only approx. owing to turbidity of solution. † Apparent increase in activity, probably due to experimental error. ‡ *M*7 solution before 2nd crystallisation gave "AFR" 71, "APR" 13·3, "PFR" 5·3.

As the details are given fully in the Experimental part, it should suffice to stress only the following points: While the use of pressure filtration facilitates the preparation of milk whey, the losses of activity during this operation were more severe than in any of the subsequent stages and greater than those reported for similar steps by other workers. We do not know yet the reasons for this; however, the loss was offset by the great advantages of the novel chromatographic treatment on solid calcium phosphate, leading to *M*5. A fourteen-fold increase in purity as measured by "APR" and a sixteen-fold decrease in volume were gained with full recovery of activity. During the dialysis (*M*5 ⟶ *M*6) coloured impurities were removed, together with some active material. A proportion of the latter could have been recovered from fractions *S*2 and *S*3 by combination with the main concentrate *M*6. This was not done in working up the run presently described.

Both the final product, *M*7, and the recrystallised sample, *M*8, appeared to be wholly crystalline under a polarising microscope. Often these coloured crystals occurred as small thin needles (*ca.* 10 μ long), sometimes bunched together in rosette-like formations (Plate 1); on other occasions larger plates were observed (Plate 2). The values for "PFR," 5·2 for *M*7 and 5·0 for *M*8 (not altered on further recrystallisation), are suggestive of a high purity, especially if compared with the best values reported in the literature, 6·15 (Morell, *loc. cit.*) and 6·2 (Corran *et al.*, *loc. cit.*, who measured E_{275}/E_{450}). There remains the question of activity. Considering the process as a whole the recovery of activity in the crystalline fraction, as represented by *M*7 was *ca.* 6% of that originally measured in the buttermilk. There is little doubt that this could be increased substantially by reworking various rejected fractions. The "APR" values are very encouraging, especially if one converts that for *M*7 into Q_{O_2} (see Experimental part), arriving at 2300 (23·5°), and compares it with Morell's figure of 694 (19°). However, the "AFR" values are not yet entirely satisfactory. They show variations between crystallisate and crystallisate (see in Table, *M*7, *M*8, and materials A and B, as previously described by Avis *et al.*, *loc. cit.*) and a slight drop from the non-crystalline *M*6 to the solution of crystalline material *M*7. As this reflects on the proportion of inactive metallo-flavoprotein to active enzyme, explained above, one has to assume that the crystals still consist of mixtures of fully potent and probably closely related inactivated xanthine oxidase, but that additional impurities have been removed to a very large extent. However, the fact that we have obtained crystalline material regularly with the properties described above shows that we have achieved a major step towards the isolation of a fully active enzyme. The questions of

PLATE 1.

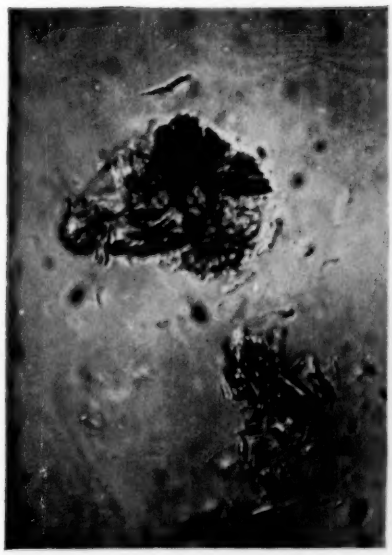


PLATE 2.

Crystalline forms of xanthine oxidase.

[*To face p.* 1102.

homogeneity of our purest fractions and their composition and catalytic properties will be treated in Parts II and III. It can be briefly stated here that sedimentation experiments with crystalline material yielded diagrams which showed an increasing degree of simplicity in comparison with those of preceding (less pure) fractions (cf. Avis *et al.*, *loc. cit.*) and with those of Corran *et al.* (*loc. cit.*). Secondly, fraction *M*7 contained FAD, iron, and molybdenum in the ratios 2·0 : 8·1 : 1·4 per unit of protein. The molybdenum ratio is higher than that reported in recent literature (cf. Richert and Westerfeld, *J. Biol. Chem.*, 1954, **209**, 179; Mackler *et al.*, *loc. cit.*) and is therefore nearer to that predicted for native xanthine oxidase (Mahler and Green, *Science*, 1954, **120**, 7). The iron ratio confirms the results of Richert and Westerfeld (*loc. cit.*).

Experimental

Purification of Milk Xanthine Oxidase (*see Scheme*, p. 1101).—(a) *Materials* (all chemicals were "AnalaR"; water was distilled and de-ionized). The buttermilk was prepared by the National Institute for Research in Dairying, Reading, by separating the cream from fresh milk; the latter was cooled overnight to 5°, then churned in the usual manner, and the resulting buttermilk passed through a cream-separator to remove any fat carried over from the churning. On one batch the buttermilk was found to contain approx. 50% of the enzyme activity originally present in the whole milk.

Calcium phosphate (cf. Polis and Shmukler, *loc. cit.*) was prepared by adding, simultaneously and with stirring, a solution of hydrated calcium chloride (1640 g.) in N/25-ammonia (5 l.) and a solution of disodium hydrogen phosphate (710 g.) in N/25-ammonia (5 l.) to water (20 l.), the solutions and water being at 70°. The precipitate was washed free from Cl ions with water by decantation during 14 days, filtered off by suction, and dried in an oven at 70°. The dried cake was gently ground to pass through a 40-mesh sieve. The adsorption power of the calcium phosphates varied from batch to batch. Analysis of three samples gave a Ca/P ratio of 1·2 [Calc. for $Ca_3(PO_4)_2$, 1·5; for $CaHPO_4$, 1·0]. One batch contained about 15% of water but did not show different adsorption power from one which was anhydrous. The final product would appear to be a mixture of $Ca_3(PO_4)_2$ and $CaHPO_4$. Buffer solutions were: (i) Phosphate (1M): from KH_2PO_4 (108·8 g.) and Na_2HPO_4 (28·36 g.) in water (to 1 l.): pH 5·8. (ii) Phosphate (0·02M): from KH_2PO_4 (2·18 g.) and Na_2HPO_4 (0·57 g.) in water (to 1 l.): pH 6·2. (iii) Phosphate (4M): from KH_2PO_4 (544 g.) and KOH (224 g.) in water (to 1 l.): pH *ca.* 9. (iv) Acetate (0·011M): from N-acetic acid (370 ml.) and sodium acetate trihydrate (99·4 g.) diluted with water to 1 l. and subsequently as required—1 vol. to 100 vols.: pH 5·1.

(b) *Enzymic precipitation of casein.* Buttermilk (25 l.) (*M*1) was warmed to 34° in a thermostat-controlled enamel-lined cast-iron vessel fitted with a pressure-tight lid and adapted as a pressure-vessel for subsequent filtration. Calcium chloride (0·5M; 250 ml.) and pancreatin (from British Drug Houses Ltd.) (40 g.) were added. After 15 min. a dense precipitate of casein was formed which was removed by straining through Nylon net (corresponding to butter muslin) (*M*2).

(c) *Filtration.* A pressure filter, of type PF40 (British Filters Ltd.), was used. The press was fitted with 13 Sterimats of grade SF/C/2, pre-coated with Hyflo Super Cel (650 g.) from a pressure vessel (British Filter No. V18) at about 5 lb./sq. in. Hyflo Super Cel (325 g.) was mixed with the material (*M*2). A starting pressure of 7 lb./sq. in. from a nitrogen cylinder was applied. The first 3 l. of the filtrate were colourless and were discarded. The rate of filtration decreased after about 10 l. had passed and a final pressure of about 28 lb./sq. in. was required before the filtration was complete (total volume 21 l.) (*M*3). The cloudy filtrate was stored for 16 hr. at 5° to allow for further hazing and refiltered through PF40 and 11 Sterimats of grade GS. The filtrate (*M*4; 20 l.) was clear and brown-yellow.

(d) *Separation of the enzyme fraction by chromatography* (all operations were at, or slightly below, 20°). A column, consisting of a piece of 6-in. Pyrex pipeline 1-ft. long, was fitted with 6 in. to $\frac{1}{8}$ in. standard adaptors at either end. A plate of stainless steel with $\frac{1}{4}$ in. perforations was clamped between the adaptor and the pipeline. In order that only the parallel-sided centre part of the pipeline should be used for the adsorbent column, a stand in the form of a crosspiece was made from $\frac{1}{4}$ in. Tufnol, $4\frac{1}{2}$ in. high; on this stand a perforated disc of $\frac{1}{4}$ in. Tufnol was placed; finally, as a support for the adsorbent a disc was cut from a Ford KC9 resin-bonded mat to fit. Calcium phosphate (*ca.* 600 g.), prepared as described above, was mixed with an equal solid volume of Celite 545 in a 5-l. beaker, and washed several times by decantation to remove any fine particles. Sufficient water was left after the final washing to prevent air bubbles

being retained. The slurry was then poured into the glass column and allowed to settle. Water was carefully layered on top of the mixture and allowed to run through. This was continued until the packing of the column was reasonably firm. Finally water was passed through at increasing pressures from 1 to 4 lb./sq. in. until a flow rate of about 4 l./hr. was obtained. Any cracks that appeared were carefully pressed out; this gave finally an adsorption column, *ca.* 6 cm. long. A layer of cotton wool was soaked in water and placed on top of the column, the whole being kept in place with a piece of stainless-steel gauze (20 mesh). The filtrate (*M*4) was cooled to 5°, adjusted to pH 6·2 (glass electrode) with 0·1N-acetic acid, and passed through the calcium phosphate column at a pressure of 4 lb./sq. in., from the pressure vessel. This gave again a flow rate of approx. 4 l./hr. The enzyme fraction developed as a brown band at the top of the column. This band diffused somewhat at the front and was not allowed to develop beyond 2 cm. from the bottom of the column, to prevent active material being lost in the effluent (*S*1). After this stage the column was washed with phosphate buffer (0·02M), until the washings gave a negative protein-test with trichloroacetic acid.

The enzyme fraction was then eluted with phosphate buffer (M), yielding fraction (*M*5) (1·22 l.). In this batch and in some others, it was necessary to subdivide filtrate (*M*4) into two parts and, after washing the adsorbent column with water until it was free from phosphate ions, to repeat the above process with the second half of fraction (*M*4). The column has been used repeatedly for chromatography of further batches, after being washed with water.

The eluate (*M*5) was precipitated with an equal volume of phosphate buffer (4M), and the precipitate filtered off in a sintered-glass funnel with the aid of Hyflo Super Cel (10 g.). The filter-cake was redissolved in a minimum of water, and the filter-aid filtered off. The final solid was washed several times with small amounts of water; the final volume with washings was 400 ml.

(e) *Purification by precipitation of contaminating proteins* (all operations at 5°). The above enzyme concentrate was dialysed in a Visking cellulose casing (size 32/32) against acetate buffer (0·01M; 40 l.). The dialysis bag was placed in a 4·5 × 75 cm. glass tube on a rocking platform, and the buffer allowed to flow through from a reservoir at a flow rate of 500 ml./hr. This treatment resulted in the formation of a copious, coloured precipitate which was centrifuged off on an angle centrifuge, a supernatant fraction (*M*6) (450 ml.) being obtained. More active material was obtained by extracting the remaining precipitate, suspending it with a hand homogenizer in acetate buffer (0·02M; 150 ml.), and re-centrifuging it, giving (*S*2). This was repeated with the same amount of buffer, giving (*S*3). The precipitate from the latter was finally taken up in aqueous sodium chloride (0·2M; 150 ml.), giving fraction (*S*4) (opaque).

(f) *Crystallisation.* Fraction (*M*6) was concentrated by perevaporation (current of air, produced by fan blown at solution in Visking cellulose casing) for 16 hr. at 5° from 450 to 320 ml., to give a 1% solution of protein as measured by the optical density at 280 mμ (higher concentrations up to 2% have been used with advantage in other batches). It was cooled to 0°; 70% v/v ethanol (160 ml.), pre-cooled in a carbon dioxide–acetone bath, was added to it from a burette fitted with a fine capillary, with sufficient stirring to ensure mixing without frothing. The solution in which a precipitate formed was set aside for 16 hr. at −6°. At the same temperature the precipitate was centrifuged off in a refrigerated centrifuge at 1300/g for 40 min. The supernatant liquid (*S*5) was not quite free from suspended precipitate. The main precipitate was dissolved in water (88 ml.), giving a total volume of 100 ml. Phosphate buffer (1M; 1 ml.) and 50% v/v ethanol (10 ml.) were added in the manner described, so that the final alcohol concentration was *ca.* 8% v/v. The solution was placed in a thermostat-controlled bath at −1° for 0·5 hr., the initial precipitate (*S*6) was centrifuged off at −1° and then redissolved in phosphate buffer (1M; 22 ml.). The supernatant liquid was seeded with material obtained from a previous batch and placed in a bath at −1°. Crystals appeared after *ca.* 12 hr. In other cases crystals appeared within 36 hr., without seeding.

After 4 days at −1° the crystals were centrifuged off at −1°, washed twice with phosphate buffer (0·01M; 70 ml. each, containing 7% v/v ethanol). The crystalline centrifugate (see Plate 1) was dissolved in aqueous 0·2M-sodium chloride (*ca.* 45 ml.) and dialysed during 16 hr. against 0·2M-sodium chloride (1 l.) in a 4·5-cm. tube on the rocking platform at 5°. The dialysis bag was emptied and washed out with small amounts of the salt solution and diluted with it to 50 ml. (*M*7).

A second crop was obtained from the centrifugation mother-liquor during 28 days at −1°. The crystals were centrifuged off and dissolved in 0·2M-sodium chloride (15 ml.) (*M*7*a*).

Part of the solution (*M*7) (10 ml.), after 28 days (see footnote ‡ to Table) at 2°, was caused to crystallise again. The enzyme was first precipitated by addition of 70% v/v ethanol (5 ml.),

then centrifuged, and redissolved in water to a final volume of 10 ml. Phosphate buffer (1M; 0·7 ml.) and 50% ethanol (1·5 ml.) were added. The immediate precipitate was centrifuged off after 10 min. at −1° and the supernatant liquid seeded and left at the same temperature for 16 hr. The crystals formed were centrifuged off and dissolved in 0·2M-aqueous sodium chloride (final volume 10 ml.) (*M*8).

Spectrophotometric Measurements and Enzyme Assay.—(a) *Materials* ("AnalaR" unless otherwise stated). (i) Phosphate buffer: Na_2HPO_4 (13·3 g.) and KH_2PO_4 (5·5 g.) dissolved in water (final vol. 2 l.), and chloroform (10 ml.) added as preservative. pH 7·1. (ii) Pyrophosphate buffer: Sodium pyrophosphate decahydrate (71·3 g.) and sodium hydrogen pyrophosphate (B.D.H. Laboratory Reagent grade) (13·3 g.) dissolved in water (final vol. 2 l.), and chloroform (10 ml.) added. pH 8·0. (iii) Xanthine (10—15 mg.; from Genatosan) dissolved in N-sodium hydroxide (2 ml.) and made up to 100 ml. with water. (iv) Buffered xanthine solution: Xanthine solution (3 ml.), N/50-hydrochloric acid (3 ml.), pyrophosphate buffer (12 ml.), and water (7 ml.), prepared weekly and stored in refrigerator.

(b) *Ultra-violet measurements of enzyme solutions at 280 and 450 mμ.* Samples were used either undiluted or after appropriate dilution with phosphate buffer; E values for the undiluted solution ($E^{1\,cm.}_{undil.}$) were calculated from $(E_{obs.} \times F)/L$ where F is the dilution factor and L the size of cell in cm.

(c) *Activity assays* (see also Kalckar, *loc. cit.*; Morell, *loc. cit.*). The sample was diluted with ice-cold pyrophosphate buffer immediately before being assayed. The dilution was arranged so that the measured rate (see below) was about 0·006—0·03/min.; appropriate dilution factors are 10—25 for buttermilk and digestion filtrates, 100—1000 for concentrates.

Buffered xanthine (2·5 ml.) was placed in a 1-cm. stoppered quartz cell, diluted enzyme solution (0·1 ml.) added, and a stop-watch started. The cell was placed in the thermostat-controlled cell compartment of the spectrophotometer (compartment constructed by Mr. A. L. Stewart; details will be published elsewhere), after its contents had been mixed by inversion. Readings at 295 mμ were taken at 0·5- or 1-min. intervals for 10 min., the first reading being taken as soon as possible after the addition of the enzyme. No comparison cell was used, and the instrument was balanced in the "check" position without any cell in place, before each reading was taken. The temperature of the circulating water was 23·5° ± 0·5°.

E_{295} was plotted against time and the slope $(\Delta E_{295}/\Delta t_{(min.)})$ of the best straight line through the experimental points was calculated. If the rate exceeded about 0·03/min. the reaction tended to slow down towards the end of the 10-min. period. Adequate temperature equilibration appears to occur within about 2 min. of placing the cell in the instrument, and temperature variation should therefore have little effect on the results. The number of units in the sample is equal to $26FV \times (\Delta E_{295}/\Delta t_{(min.)})$, where V is the volume of the sample in litres, F is the dilution factor used in preparing the enzyme solution for assay, and 26 represents the further dilution which takes place in the assay mixture. (N.B.: The final concentrations in the assay solution are as follows: xanthine *ca.* 10^{-4}M, pyrophosphate 0·05M, final pH 8·2.) Q_{O_2} is related to "APR" as described previously (Avis *et al.*, *loc. cit.*), *viz.*, Q_{O_2} = "APR" × 152.

Xanthine Oxidase and Beer's Law.—A solution of xanthine oxidase ("PFR" = 8·1) was dialysed against 0·01M-sodium chloride and centrifuged to give a clear solution, which gave the following readings at 450 mμ:

Solution	Light path (cm.)	Corr. reading	Calc. $E^{1\,cm.}_{undil.}$	Approx. concn. (%)
Undiluted	0·5	1·142	2·28	1·7
Dil. × 3	0·5	0·381	2·29	0·6
Dil. × 25	4	0·362	2·26	0·07

Dilutions were carried out as described above, and the approximate concentrations calculated from the E_{280} by using the $E^{1\%}_{1\,cm.}$ value given previously (Avis *et al.*, *loc. cit.*).

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Studies on Fructosans. Part VI. The Degradation of Fructosans in Aqueous Solution.*

By G. O. Aspinall and R. G. J. Telfer.

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It has been shown that the degradation of fructosans in hot aqueous solution involves the formation of small quantities of acidic materials, which cause the fructosans to undergo slow hydrolysis. The oligosaccharides, formed from the partial breakdown of the fructosan from perennial rye-grass, have been examined. The isolation of sucrose provides further evidence that in the grass levans the chains of fructofuranose residues are terminated by a non-reducing glucopyranose unit.

It has been shown in Parts II, III, and IV of this series (Arni and Percival, *J.*, 1951, 1822; Laidlaw and Reid, *J.*, 1951, 1830; Aspinall, Hirst, Percival, and Telfer, *J.*, 1953, 337) that fructosans are degraded in aqueous solution at 100° and that after several hours the products consisted of fructose, glucose, and a series of oligosaccharides, amongst which sucrose was suspected. The present investigation was undertaken to study such degradations in greater detail and to obtain further information about the role of glucose in fructosan molecules. The isolation of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose from the hydrolysis of methylated inulin (Hirst, McGilvray, and Percival, *J.*, 1950, 1297) and of the methylated levan from cocksfoot grass (*Dactylis glomerata*) (Part IV, *loc. cit.*) showed that terminal non-reducing glucopyranose residues are present in these fructosans. Although, in the former case, evidence was also obtained for the presence of 2 : 4 : 6-tri-*O*-methyl-D-glucose in the hydrolysate of the methylated polysaccharide, it seems probable that this sugar arose from incomplete methylation as it has been shown by periodate oxidation (Aspinall and Telfer, *Chem. and Ind.*, 1953, 490) that no 1 : 3-linked glucose residues are present in inulin. Biogenetic evidence from the investigations of Bacon and Edelman (*Biochem. J.*, 1951, **48**, 114; **49**, 446, 529) and of Dedonder (*Compt. rend.*, 1950, **230**, 549, 997; 1951, **231**, 790; **232**, 1134, 1142) indicates that fructosans are built up in the plant from sucrose by enzymic transfructosidation, and thus provides further support for the view that terminal glucopyranose residues are present in fructosan molecules linked to the penultimate fructofuranose residues as in sucrose.

The degradation of two fructosans has been studied. Inulin was extracted from dahlia tubers with hot water and purified by deposition from aqueous solution on cooling. The levan from perennial rye-grass (*Lolium perenne*) was isolated from the sample of grass used by Laidlaw and Reid (*loc. cit.*) in their investigations. Both fructosans gave fructose and small quantities of glucose (2·8% and 2·0%, respectively) on hydrolysis. The degradation in aqueous solution at 100° was followed by observing changes in pH and optical rotation, and by periodic chromatographic examination of the products. The same general pattern of breakdown was observed with both fructosans; a gradual fall in pH was accompanied by a change in optical rotation with the formation at first of oligosaccharides and finally of fructose and glucose, complete breakdown occurring after about 24 hours. In addition, chromatographic evidence showed the presence of small quantities of difructose anhydrides. These substances were formed more readily from the hydrolysis of inulin. A parallel experiment showed that sucrose undergoes similar breakdown in aqueous solution at 100°, no sucrose being present after 30 hours. Typical data for the degradation of inulin are recorded in the Table.

The fall in pH together with chromatographic indication of the presence of acidic breakdown products showed that degradation of the fructosans was, at least in the later stages, an acid hydrolysis. When inulin was heated in phosphate buffer (pH 6·8) no oligosaccharides or monosaccharides were formed, although the dark coloration of the

* A preliminary account of some of the following results has appeared elsewhere (*Chem. and Ind.*, 1952, 1244). Part V, *J.*, 1954, 2364.

solution showed that some decomposition had occurred. It was also shown that the presence of atmospheric oxygen is an important factor in initiating the degradation; when inulin was heated in aqueous solution through which nitrogen was bubbled the breakdown occurred much more slowly, and after 60 hours considerable quantities of oligosaccharides were still present.

Preliminary chromatographic examination of the products of partial degradation of the levan from perennial rye-grass showed that an optimum yield of oligosaccharides, travelling on the chromatogram at the same rate as or slower than sucrose could be obtained

The degradation of inulin in aqueous solution.

	Time (hr.)	pH	$[\alpha]_D$	Paper chromatography * U	O	D + T	F	G	DFA
Inulin in 3% soln. at 100°	0	6·28	−40·3°	3	—	—	—	—	—
	4	5·14	−39·3	3	2	1	—	—	—
	8	4·40	−45·9	3	2	2	1	—	—
	12	3·93	−60·9	3	2	2	3	1	—
	16·5	3·70	−79·1	—	1	2	3	1	1
	25	3·35	−84·2	—	—	1	3	1	2
Inulin in 3% soln. at 100° in N_2	10	6·11	−44·6	3	1	—	—	—	—
	25	5·36	−47·7	3	2	1	1	—	—
	42	4·88	−53·6	3	2	2	2	—	—
	52	4·66	−67·1	2	2	2	3	1	1
	75	4·24	−78·5	—	1	1	3	1	2
Inulin in phosphate buffer (pH 6·80)	0	6·80	−38·5	3	—	—	—	—	—
	16	6·76	−39·2	3	—	—	—	—	—
	32	6·48	−40·0	3	—	—	—	—	—

* Numbers denote relative intensity, 3 denoting the greatest. U, unchanged fructosan; O, higher oligosaccharides; D + T, di- and tri-saccharides; F, fructose; G, glucose; DFA, difructose anhydrides.

if the reaction was stopped after 6 hours. The oligosaccharides, which, from their rate of movement on the chromatogram, appeared to be di-, tri-, and tetra-succharides, were separated chromatographically, eluted from the paper, and hydrolysed. The amounts of fructose and glucose thus obtained suggested that the " spots " on the chromatogram contained mixtures of oligosaccharides, each spot containing a sugar giving only fructose on hydrolysis, in addition to a sugar giving both fructose and glucose. Further investigation showed that each spot could be at least partially resolved into two components. The levan was heated at 100° in aqueous solution for 6 hours and the hydrolysis products were fractionated successively on charcoal–Celite (Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677) by elution with water and aqueous ethanol, and by partition chromatography on cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511). In this way several oligosaccharide-containing fractions were obtained. In some cases, these fractions required further separation by partition on filter sheets before the individual components were isolated.

From these extensive fractionations four sugars of particular interest were isolated: (i) a reducing disaccharide, which gave only fructose on both acid and enzymic hydrolysis; (ii) a reducing trisaccharide, which gave only fructose on acid hydrolysis, and fructose and the afore-mentioned disaccharide on incubation with yeast invertase; (iii) sucrose (identified by its physical constants and by conversion into the octa-acetate); and (iv) a non-reducing trisaccharide, which on hydrolysis gave fructose and glucose in the ratio of 2 : 1, and on partial hydrolysis gave fructose and sucrose together with traces of glucose and the reducing disaccharide. In view of their derivation from a fructosan of known general structure, it is highly probable that the reducing di- and tri-saccharides contain D-fructofuranose residues linked through positions $C_{(2)}$ and $C_{(6)}$, and experiments to establish the mode of linkage are at present in progress. Again, it is probable that the non-reducing tris accharide is identical with the trisaccharide, kestose, synthesised from sucrose by yeast invertase and shown by Albon, Bell, Blanchard, Gross, and Rundell (*J.*, 1953, 24) to be *O*-α-D-glucopyranosyl-(1→2)-*O*-β-D-fructofuranosyl (6→2)-β-D-fructofuranoside.

Evidence was also obtained for the presence in very small yield of a fructosylglucose. It is doubtful, however, if this sugar is of structural significance and it is likely that the sugar arose either as a reversion product or more probably by epimerisation from the reducing disaccharide during prolonged contact with the pyridine-containing chromatographic solvent. In a control experiment, fructose and glucose were heated together in aqueous solution but no evidence could be obtained for the formation of reversion products.

The isolation of sucrose from the partial hydrolysis of the levan from perennial ryegrass provides conclusive evidence that glucose residues are present in this polysaccharide as an integral part of the molecule. Schlubach and Holzer (*Annalen*, **1953**, **578**, 207) claim to have isolated a fructosan from *Lolium perenne* devoid of glucose residues, and it is, indeed, possible that some fructosan molecules may contain no glucose. The present investigation, however, stresses the need for the utmost caution in handling these extremely labile polysaccharides lest inadvertent scission of the fructosan chain results in loss of the glucose-containing moiety. The evidence from both structural investigations and studies of enzymic transfructosidation shows that the majority, at least, of fructosan molecules, both of the inulin and of the levan type, contain terminal glucose residues linked as in sucrose.

Experimental

Paper partition chromatography was carried out on Whatman No. 1 filter paper with the solvent systems: (*A*) butan-1-ol–benzene–pyridine–water (**5 : 1 : 3 : 3**; v/v; top layer); (*B*) butan-1-ol–ethanol–water (**4 : 1 : 5**; v/v; top layer); and (*C*) ethyl acetate–acetic acid–water (**3 : 1 : 3**; v/v; top layer). Sprays of aqueous aniline oxalate and naphtharesorcinol in hydrochloric acid were used to detect aldoses and ketoses, respectively.

Isolation of the Polysaccharides.—(a) *Inulin.* Dahlia tubers (variety "Crimson Flag") were extracted by Hirst, McGilvray, and Percival's method (*loc. cit.*). The inulin, which separated on cooling from aqueous solution, had $[\alpha]_D^{16}$ −40·3° (*c*, 2·4 in H_2O). Chromatographic examination of the hydrolysate (Hirst and Jones, *J.*, **1949**, **1659**; Duff and Eastwood, *Nature*, **1950**, **165**, **848**) in solvent *C* showed the presence of fructose (97·2%) and glucose (2·8%).

(b) *Levan.* The fructosan from *Lolium perenne* was isolated as described by Laidlaw and Reid (*loc. cit.*).

Degradation of Inulin in Aqueous Solution.—Inulin (1·5—2·0 g.) was dissolved in water (50 c.c.), and the solution heated on the water-bath and examined periodically for changes in optical rotation and pH, samples being withdrawn for chromatographic examination in solvent *A*. The results are given in the Table. In some cases, oligosaccharides, which appeared, from their rate of movement, to be di-, tri-, and tetra-saccharides, were eluted from the chromatogram and hydrolysed with aqueous 1% oxalic acid, and the hydrolysates examined chromatographically in solvent *C*. Fructose and glucose were present in each hydrolysate, but visual estimates of the ratio of the sugars suggested that each "discrete spot" on the chromatogram contained two oligosaccharides, one giving fructose and glucose and the other giving only fructose on hydrolysis. The inulin solution was also tested periodically with the ammonium thiocyanate–ferrous ammonium sulphate reagent (Young, Vogt, and Nieuland, *Ind. Eng. Chem. Anal.*, **1936**, **8**, 198), but in no case were hydroperoxides present.

Inulin (1·5 g.) was heated in phosphate buffer solution (50 c.c.; pH 6·8) and the reaction was followed as described previously. Although the solution darkened considerably no breakdown products could be detected chromatographically. The degradation of inulin in unbuffered aqueous solution through which nitrogen was bubbled was similar to that in air but much slower (see Table).

Degradation of Levan in Aqueous Solution.—The degradation of *Lolium perenne* levan in aqueous solution was followed in the manner described for inulin, and the reaction pattern was essentially similar. In a typical experiment the following changes were observed: $[\alpha]_D^{16}$ −42·8° (initial value), −36·3° (4 hr.), −48·6° (8 hr.), −72·6° (16 hr.), −79·6° (24 hr., const.); pH 5·01 (initial value), 4·48 (4 hr.), 4·11 (8 hr.), 3·54 (16 hr.), 3·20 (24 hr.). Chromatographic examination of the product in solvent *B*, followed by development with methyl-red–methylene-blue (Conway and Byrne, *Biochem. J.*, **1933**, **27**, **419**), showed the presence of two acids, one of which travelled at the same rate as lactic acid.

Degradation of Sucrose in Aqueous Solution.—A solution of sucrose (1·7 g.) in water (50 c.c.) was heated on the water-bath. The following changes were observed: $[\alpha]_D^{16}$ +65·3° (initial

value) ⟶ −12·3° (36 hr., const.); pH 5·98 (initial value) ⟶ 3·32 (36 hr.). Chromatographic examination of the solution showed gradual breakdown with the formation of glucose and fructose, and after 30 hr. sucrose could no longer be detected. Two acids were also detected.

Large-scale Degradation of Levan and Separation of Oligosaccharides.—A solution of the levan (50 g.) in water (1·4 l.) was heated on the water-bath for 6·5 hr. {$[\alpha]_D$ −41·1° ⟶ −48·6° (6 hr.); pH 4·40 ⟶ 4·08 (6 hr.)}. The cooled solution was neutralised with barium carbonate, and the clear filtrate was concentrated; chromatographic examination of the syrup showed the presence of fructose and a series of oligosaccharides.

A solution of the syrup in water (500 c.c.) was poured on to charcoal–Celite (38·5 × 4·6 cm.) (Whistler and Durso, *loc. cit.*). The aqueous eluate, however, contained oligosaccharides in addition to monosaccharides and appropriate portions were, therefore, combined to give three fractions. Fraction *A* (10·2 g.) was shown chromatographically to contain only fructose and glucose and was not examined further. Fraction *B* (23·0 g.) contained fructose, glucose, sucrose, and a sugar having $R_{sucrose}$ 1·18. Fraction *C* (3·2 g.) contained fructose, sucrose, and sugars having $R_{sucrose}$ 1·18 and 0·71. Elution of the column with 50% aqueous ethanol gave fraction *D* (14·1 g.), which contained a sugar having $R_{sucrose}$ 0·71 and slower-moving oligosaccharides. Fraction *B* was further separated on charcoal–Celite (62 × 4·5 cm.), elution with water giving fraction *B*(i) (17·2 g.) containing fructose and glucose (trace), and elution with 5% aqueous ethanol giving fraction *B*(ii) (4·42 g.) containing a sugar having $R_{sucrose}$ 1·18 and *B*(iii) (0·546 g.) containing sucrose and sugars having $R_{sucrose}$ 1·18 and 0·85. Fraction *C* was separated on cellulose (70 × 3 cm.), solvent *A* being used, to give fractions containing fructose, glucose, and substances travelling on the chromatogram faster than fructose (probably difructose anhydrides), four oligosaccharide-containing fractions (1—4) and a fraction *C*(i) (0·914 g.) containing sucrose and the sugar of $R_{sucrose}$ 1·18. Fractions *B*(iii) and *C*(i) were combined and separated on cellulose (100 × 1·7 cm.) to give fractions containing glucose, fructose, and (probably) difructose anhydrides, and two further oligosaccharide-containing fractions (5 and 6). In some fractions traces of an unidentified substance were present; this travelled on the chromatogram considerably faster than fructose and gave a blue coloration with naphtharesorcinol and hydrochloric acid.

Examination of Oligosaccharide-containing Fractions.—Fraction 1. The syrup (0·442 g.), which reduced Fehling's solution and ammoniacal silver nitrate, had $[\alpha]_D^{17}$ −20·8° (*c*, 4·0 in H_2O) and $R_{sucrose}$ 1·18 in solvent *A*. Both mild acid hydrolysis and incubation with yeast invertase (B.D.H. "Invertase Concentrate") gave only fructose. The rate of movement on the chromatogram indicated that the sugar was a disaccharide, and its derivation from a fructosan of known general structure suggests that the sugar was 6-*O*-β-D-fructofuranosyl-D-fructofuranose (referred to as fructobiose).

Fraction 2. Chromatographic examination of the syrup (0·242 g.) showed the presence of four sugars, probably (*a*) fructobiose, (*b*) sucrose, (*c*) fructosylglucose ($R_{sucrose}$ 0·85), (*d*) fructotriose. Separation of small quantities of the sugars was effected on the chromatogram by using solvent *A*, (*a*), (*c*), and (*d*), but not (*b*), reducing ammoniacal silver nitrate. On mild acid hydrolysis or incubation with yeast invertase (*a*) and (*d*) gave only fructose, while (*b*) and (*c*) gave glucose and fructose.

Fraction 3. The chromatographically pure syrup (0·393 g.) had $R_{sucrose}$ 0·71 in solvent *A*. The sugar had $[\alpha]_D^{16}$ −21·1° (*c*, 3·18 in H_2O) and reduced Fehling's solution and ammoniacal silver nitrate. Mild acid hydrolysis gave only fructose, and incubation with yeast invertase gave fructose and fructobiose. It seems probable that the sugar was 6-*O*-β-D-fructofuranosyl-6-*O*-β-D-fructofuranosyl-β-D-fructofuranose (referred to as fructotriose).

Fraction 4. Chromatographic examination showed the presence of two trisaccharides and separation on filter sheets with solvent *A* gave fractions (*e*) (450 mg.), having $R_{sucrose}$ 0·71 (identical with fructotriose), and (*f*) (40 mg.), having $R_{sucrose}$ 0·60. Fraction (*f*) and $[\alpha]_D^{18}$ +24° (*c*, 0·5 in H_2O) and was non-reducing towards Fehling's solution and ammoniacal silver nitrate. Incubation with yeast invertase gave glucose and fructose, and quantitative estimation (Hirst and Jones, *loc. cit.*) of the acid hydrolysate showed glucose and fructose to be present in the ratio 1 : 2. A portion of the syrup (10 mg.) was dissolved in water (5 c.c.), and the solution was heated at 100° with Amberlite resin IR-100 (0·5 g.). After 30 min. chromatographic examination showed fructose and sucrose, together with traces of glucose and fructobiose. Hydrolysis to fructose and glucose was complete after 1 hr. It is probable that the sugar was *O*-α-D-glucopyranosyl-(1→2)-*O*-β-D-fructofuranosyl (6→2)-β-D-fructofuranoside (kestose) (Albon, Bell, Blanchard, Gross, and Rundell, *loc. cit.*). Albon *et al.* record $[\alpha]_D^{20}$ +27·3° for the crystalline sugar.

Fraction 5. The syrup (0·553 g.) contained sucrose and sugars having $R_{sucrose}$ 1·18 and 0·85. The sugars were separated on filter sheets, solvent *A* being used, to give fractions 5(*a*) (228 mg.), which travelled on the chromatogram at the same rate as fructobiose, 5(*b*) (287 mg.), which travelled on the chromatogram at the same rate as sucrose, and 5(*c*) (31 mg.). Fraction 5(*b*) crystallised from aqueous ethanol and had m. p. (and mixed m. p. with sucrose) 184—185° (Found: C, 42·2; H, 6·4. Calc. for $C_{12}H_{22}O_{11}$: C, 42·1; H, 6·4%). A sample was hydrolysed with aqueous 1% oxalic acid {$[\alpha]_D$ +59° ⟶ −24° (1 hr., const.)}, and quantitative estimation (Hirst and Jones, *loc. cit.*) of the hydrolysate showed glucose and fructose to be present in the ratio 1 : 1·05. The identity of the sugar was confirmed by an *X*-ray powder photograph (by courtesy of Dr. C. A. Beevers), which was identical with that of sucrose, and by conversion into sucrose octa-acetate, m. p. and mixed m. p. 72—73°, η_D^{20} (fused crystals) 1·4602, $[\alpha]_D^{17}$ +60° (*c*, 1·1 in $CHCl_3$) (Found: C, 49·5; H, 5·8; Ac, 50·3. Calc. for $C_{28}H_{38}O_{19}$: C, 49·5; H, 5·6; Ac, 50·7%).

Fraction 6. The syrup (31 mg.) was combined with fraction 5(*c*), both fractions containing a sugar having $R_{sucrose}$ 0·85 in solvent *A* together with traces of other sugars. The sugar reduced Fehling's solution and ammoniacal silver nitrate, and gave glucose and fructose on treatment with yeast invertase. Quantitative estimation of the acid hydrolysate showed glucose and fructose to be present in the ratio of 1 : 1·27. Reduction of alkaline hypoiodite (55% of theoretical for a disaccharide) showed that the major component of the syrup was a fructosylglucose.

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The Preparation of Aromatic Aldehydes by Means of the Dinitrogen Tetroxide Reagent.

By B. O. Field and J. Grundy.

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A variety of substituted benzyl alcohols has been converted into the corresponding aldehydes by means of dinitrogen tetroxide solutions. The excellent yields and the simplicity of the technique show the reaction to be a valuable general preparative method for aromatic aldehydes.

Cohen and Harrison (*J.*, 1897, **71**, 1057) first observed the conversion of a benzyl alcohol into a benzaldehyde by chloroform solutions of dinitrogen tetroxide. The present work is an investigation of the scope and utility of the reaction. Benzyl alcohols carrying electronically and sterically different substituents have been examined; excellent yields in all cases establish the reaction in its generality as superior to most available preparative methods (see, *e.g.*, Wagner and Zook, "Synthetic Organic Chemistry," Wiley and Sons, Inc., New York, p. 279). For instance, Stephen's synthesis gives reduced yields when *ortho*-substituents are present, and the promising elaboration of the Sommelet reaction has been found of diminished value because of the adverse effect of electron-attracting substituents (Angyal, Morris, Tetaz, and Wilson, *J.*, 1950, 2141).

When a solution of dinitrogen tetroxide in chloroform or carbon tetrachloride and a solution of a benzyl alcohol are mixed, each at 0°, the initially homogeneous and brown mixture, when kept at room temperature, becomes opaque owing to separation of water. After a further period the mixture becomes green owing to formation of dinitrogen trioxide, and the colour deepens as the reaction proceeds. It is therefore suggested that the reaction

proceeds by homolytic attack of $\cdot NO_2$ radicals on the α-methylene group of the benzyl alcohol, the nitro-alcohol then decomposing to the aldehyde:

$$C_6H_5\cdot CH_2\cdot OH + 2NO_2\cdot \longrightarrow C_6H_5\cdot CH(OH)\cdot NO_2 + HNO_2[H_2O + N_2O_3] \longrightarrow C_6H_5\cdot CHO + HNO_2[H_2O + N_2O_3]$$

The benzyl alcohols were obtained from both the acid chlorides and the methyl esters of the appropriate acids by reduction with excess of lithium aluminium hydride. In a few cases ethyl esters were tried but methyl esters gave better results and were subsequently used. *m*-Nitrobenzyl alcohol was obtained by Lock's method (*Ber.*, 1930, **63**, 855), but in our hands the reaction was by no means as successful as claimed. The techniques of reduction were extensively examined and finally the reductions were done in ether solution, a four-fold excess of hydride being added, as a suspension–solution, with stirring. A recent method of this type (Tadros, Ekladius, and Sakla, *J.*, 1954, 2353) was tried but gave considerable trouble. The use of four-fold excess of solid hydride resulted in caking on the walls of the flask, making the reaction difficult to control and frequently dangerous. The use of dilute (1 : 1) acetic acid was not as effective as that of 5% (w/w) sulphuric acid in dissolving aluminium hydroxide and permitting clean separation of the ether phase. The results of the reductions are given in Table 1.

TABLE 1. *Yields of alcohols.*

R in R·C_6H_4·CH_2·OH	Yield (%): from acid chloride	Yield (%): from methyl ester	R in R·C_6H_4·CH_2·OH	Yield (%): from acid chloride	Yield (%): from methyl ester
o-Me	90	97	*m*-Br	92	95
m-Me	92	95	*p*-Cl	96	98
p-Me	94	98	*o*-OMe	93	98
o-Cl	96	98	*p*-OMe	94	98
o-Br	95	97	(α-Naphthylmethanol)	92	96
o-I	90	94			

The acids required were obtained by standard methods, as were the acid chlorides and esters. Several reported methods (*e.g.*, Cattelain, *Bull. Soc. chim.*, 1927, **41**, 1547) claim the preparation of pure *o*-iodobenzoic acid, but this substance could not be obtained colourless by a direct method. Pure white acid was obtained by converting the coloured product into the acid chloride or *via* the acid chloride into the methyl ester, which was then hydrolysed (cf. Cohen and Raper, *J.*, 1904, **85**, 1272).

TABLE 2. *Yields of aldehydes.*

Aldehyde	Yield (%)	Aldehyde	Yield (%)	Aldehyde	Yield (%)
o-Tolualdehyde	95	*o*-Bromobenzaldehyde	94	*o*-Methoxybenzaldehyde	96
m-Tolualdehyde	98	*o*-Iodobenzaldehyde	94	*p*-Anisaldehyde	97
p-Tolualdehyde	98	*m*-Bromobenzaldehyde	96	*m*-Nitrobenzaldehyde	98
o-Chlorobenzaldehyde	96	*p*-Chlorobenzaldehyde	98	1-Naphthaldehyde	91

TABLE 3. *Derivatives prepared for characterisation.*

R in R·C_6H_4·CHO	Derivative	M. p. of deriv.	Formula	N (%) Found	N (%) Calc.
o-Me	2 : 4-Dinitrophenylhydrazone	193—194°	$C_{14}H_{12}O_4N_4$	18·5	18·6
m-Me	,, ,,	211—212	$C_{14}H_{12}O_4N_4$	18·2	18·6
p-Me	,, ,,	233—234	$C_{14}H_{12}O_4N_4$	18·5	18·6
o-Cl	,, ,,	208—209	$C_{13}H_8O_4N_4Cl$	17·8	17·5
o-Br	Semicarbazone	215—216	$C_8H_8ON_3Br$	17·2	17·3
o-I	,,	204—205	$C_8H_8ON_3I$	14·4	14·5
m-Br	,,	204—205	$C_8H_8ON_3Br$	17·1	17·3
p-Cl	*p*-Nitrophenylhydrazone	218—219	$C_{13}H_{10}O_2N_3Cl$	15·4	15·2
o-OMe	,,	204—205	$C_{14}H_{13}O_3N_3$	15·3	15·1
p-OMe	2 : 4-Dinitrophenylhydrazone	254—255	$C_{14}H_{12}O_5N_4$	17·8	17·7
m-NO_2	,,	291—292	$C_{13}H_9O_5N_5$	21·0	21·1
(1-Naphthaldehyde)	*p*-Nitrophenylhydrazone	234—235	$C_{17}H_{13}O_2N_3$	14·3	14·4

Various derivatives were made for the identification of the aldehydes prepared, but m. p.s were frequently erratic; *e.g.*, even slight impurities in the starting materials gave

2 : 4-dinitrophenylhydrazones whose m. p.s were not sharp, although analyses were always good. Only those 2 : 4-dinitrophenylhydrazones recorded were easily obtained, indicating that these derivatives are not as suitable as generally believed. The derivatives shown in Table 3 were found satisfactory for identification.

Experimental

Preparation of the Dinitrogen Tetroxide Reagent.—(*a*) Bulk dinitrogen tetroxide was obtained as a liquid by Partington and Park's method (*J.*, **1924**, **125**, 74). The crude liquid was twice distilled over phosphoric oxide and then dissolved in chloroform or carbon tetrachloride (1 g. per 3 ml. of solvent), this concentration being found best for the oxidation. The solution was stored in glass with a secured stopper, and immediately before use the container was cooled in ice for safety in opening and to avoid losses of dinitrogen tetroxide.

(*b*) For a single oxidation a limited amount of dinitrogen tetroxide was prepared by quantitative thermal decomposition of lead nitrate (Dodd and Robinson, "Experimental Inorganic Chemistry," Elsevier, p. 234). The gas evolved was dissolved in the solvent cooled to $-10°$ to $-20°$. The solution thus obtained was diluted as required.

Preparation of Benzyl Alcohols.—The ester or acid chloride (0·2 mole) was dissolved in pure ether (100 ml.) and kept in a flask fitted with a wide-bore condenser and a stirrer. The solution was cooled to $-10°$, and a suspension–solution of lithium aluminium hydride (0·4 mole) in pure ether (300 ml.) added portionwise *via* the condenser. The mixture was then refluxed on the steam-bath for 2 hr., then cooled to $-10°$, and wet ether (50 ml.) was added with stirring. (This preliminary addition of wet ether seemed to be of value in initiating the decomposition of excess of hydride and making the subsequent decomposition with water smoother). The remaining hydride was decomposed by dropwise addition of water, stirring being continued. There was generally considerable loss of ether during the decomposition, and this was made good when decomposition was complete. The mixture was shaken with a slight excess of 5% (w/w) sulphuric acid, and the ether layer was separated, washed with 10% sodium hydrogen carbonate solution then with water and finally dried (Na_2SO_4). Although the alcohols thus obtained were essentially pure they were distilled or recrystallised as applicable; yields are given in Table 1.

m-Nitrobenzyl alcohol. To *m*-nitrobenzaldehyde (15·1 g.) was added 35% (w/w) sodium hydroxide solution (30 g.). The mixture was vigorously shaken until the temperature reached 45°, and then diluted with water and extracted with ether; the product obtained from the ether solution gave, after recrystallisation from ethanol (ice-cooling), 3·2 g. of *m*-nitrobenzyl alcohol, m. p. 26—27°.

Identification of Alcohols.—The alcohols were identified by oxidation to the corresponding acids, these in turn being identified by mixed m. p. The alcohol (1 g.) was added to a solution of potassium permanganate (3 g.) in 5% sodium carbonate solution (75 ml.), and the mixture refluxed for 15—30 min. The acids were isolated in the usual way, in excellent yield. For the oxidation of the methyl and *o*-iodobenzyl alcohols only a slight excess of permanganate was employed.

Preparation of Aldehydes.—The alcohol (0·1 mole) was dissolved in 2—3 times its volume of dry solvent, and the solution cooled to 0°. An ice-cold solution of dinitrogen tetroxide (0·13 mole) was then added, and the mixture left for 15 min. at 0°, and then stored overnight at room temperature in a glass-stoppered flask. The resulting green mixture was finally distilled (oil-bath) under a suitably reduced pressure to remove excess of reagent, solvent, and dinitrogen trioxide. The residue, whether solid or liquid, was taken up in ether and the solution washed with 10% sodium hydrogen carbonate solution, then with water and dried (Na_2SO_4). The aldehydes were isolated from the ether solution in the usual way. The yields are recorded in Table 2.

The Technical College, Blackburn. [*Received, November 19th* 1954.]

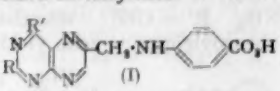
Polyazanaphthalenes. Part II. Attempted Synthesis of Some Analogues of Pteroic Acid.*

By PHYLLIS D. LANDOR and H. N. RYDON.

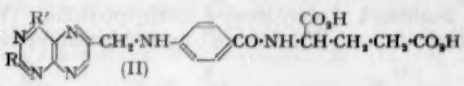
[Reprint Order No. 5930.]

Attempts to prepare a series of analogues of pteroic acid were frustrated by the failure of the standard synthetic methods when applied to 4 : 5-diaminopyrimidines other than 2 : 4 : 5-triamino-6-hydroxy- and 2 : 4 : 5 : 6-tetra-amino-pyrimidine. Unsuccessful attempts were also made to prepare the required analogues from 4-amino-5-nitrosopyrimidines. A number of 7-hydroxy-6-methylpteridines were prepared by condensing 4 : 5-diaminopyrimidines with ethyl oxaloacetate and two of these were converted into 7-hydroxy-derivatives of the required pteroic acid analogues; attempts to remove the 7-hydroxy-group failed. Condensation of 2 : 4 : 5-triamino-6-hydroxypyrimidine with hydroxyiminoacetone in sodium sulphite solution afforded 2 : 6-diamino-4-hydroxy-7-methylpteridine.

THE work described in this paper had as its objective the synthesis of analogues of pteroic acid (I; R = NH_2, R′ = OH) and folic acid (II; R = NH_2, R′ = OH), in which R and R′ were varied; † these two growth factors are over-provided with possible points of attachment to enzyme molecules and it was hoped that correlation of biological activity with variations in R and R′ would yield information as to the participation of the amino- and hydroxy-groups normally present in these positions in attachment of the growth factors to enzymes.



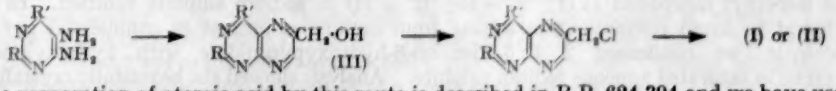
(I)



(II)

No great difficulty was expected in preparing the required analogues by the obvious modification of the method (condensation of 2 : 4 : 5-triamino-6-hydroxypyrimidine with αβ-dibromopropaldehyde and *p*-aminobenzoic or *p*-aminobenzoylglutamic acid) used originally for the synthesis of pteric acid and folic acid (Waller *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 19), since aminopterin (II; R = R′ = NH_2) is satisfactorily prepared by applying this method to 2 : 4 : 5 : 6-tetra-aminopyrimidine (Seeger, Cosulich, Smith, and Hultquist, *ibid.*, 1949, **71**, 1753). However, no pteridine could be isolated from the products obtained by applying this reaction to 4 : 5-diamino-6-hydroxy-, 4 : 5-diamino-6-hydroxy-2-methyl-, 4 : 5 : 6-triamino-2-hydroxy-, and 4 : 5 : 6-triamino-6-mercapto-pyrimidine, even in the presence of sodium dichromate, which has been shown (Boothe *et al.*, *ibid.*, p. 2304) to increase the yield. In the first two cases mentioned, light-absorption data indicated the presence of a small amount of pteridine in the crude product.

Condensation of 2 : 4 : 5-triamino-6-hydroxypyrimidine with dihydroxyacetone in the presence of hydrazine (Forrest and Walker, *J.*, 1949, 79, 2077; Weygand, Wacker, and Schmied-Kowarzik, *Chem. Ber.*, 1949, **82**, 25; Karrer and Schwyzer, *Helv. Chim. Acta*, 1949, **32**, 423, 1041) leads to the 6-hydroxymethyl compound (III; R = NH_2, R′ = OH), which can be converted into pteroic and folic acid, thus:



(III)

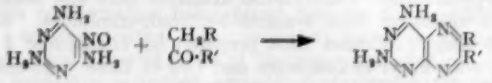
The preparation of pteroic acid by this route is described in B.P. 624,394 and we have used it to prepare pure pteroic acid in excellent yield. In spite of its success with 2 : 4 : 5-triamino-6-hydroxypyrimidine, however, this method failed completely with 4 : 5-diamino-6-hydroxy-, 4 : 5-diamino-6-hydroxy-2-methyl-, 2 : 4 : 5-triamino-, 2 : 4 : 5-triamino-6-methyl-, and 4 : 5 : 6-triamino-2-hydroxy-pyrimidine, none of which yielded any pteridine.

* Part I, Leese and Rydon, *J.*, 1955, 303.

† Since our work was completed, Brown (*J.*, 1953, 1644) has described the synthesis of deaminofolic acid (II; R = H, R′ = OH).

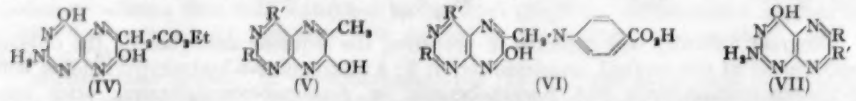
In view of the ready availability of 4-amino-5-nitrosopyrimidines (Landauer and Rydon, *J.*, 1953, 3721) we next investigated two methods requiring these compounds as starting materials. Condensation of dihydroxyacetone with 2 : 4-diamino-6-hydroxy-5-nitrosopyrimidine has been reported (U.S.P. 2,461,503; Swiss P. 253,475) to give pure 2-amino-4-hydroxy-6-hydroxymethylpteridine (III; R = NH_2, R′ = OH); under the conditions we employed, however, the main product was the isomeric 2-amino-4-hydroxy-7-hydroxymethylpteridine and this route was not investigated further.

Timmis (*Nature*, **1949**, **164**, 139) synthesised a number of pteridines by condensing 4-amino-5-nitrosopyrimidines with ketones, *e.g.* :



This route is attractive, owing to its apparent lack of ambiguity, and we sought to adapt it to our purposes. However, no pteridine could be isolated from the reaction products of 2 : 4-diamino-6-hydroxy-5-nitrosopyrimidine and propaldehyde diethyl acetal, β-chloropropaldehyde diethyl acetal, or the condensation product of the latter with *p*-aminobenzoic acid; nor was any pteridine produced when 2 : 4-diamino-6-hydroxy-5-nitrosopyrimidine was heated with ethyl sodioacetoacetate, despite the success of the analogous reaction for the preparation of 1 : 4 : 5-triazanaphthalenes (Leese and Rydon, *J.*, 1955, 303).

Tschesche, Köhncke and Korta (*Z. Naturforsch.*, 1950, **5***b*, 132; *Chem. Ber.*, 1951, **84**, 485) condensed 2 : 4 : 5-triamino-6-hydroxypyrimidine with ethyl oxaloacetate and obtained a good yield of the ester (IV), which underwent ready hydrolysis and decarboxylation to 2-amino-4 : 7-dihydroxy-6-methylpteridine (V; R = NH_2, R′ = OH); side-chain bromination of (V), followed by condensation with *p*-aminobenzoylglutamic acid, yielded



7-hydroxyfolic acid. This reaction we have found to be widely applicable to 4 : 5-diaminopyrimidines and we have used it to prepare 4 : 7-dihydroxy- (V; R = H, R′ = OH), 2-amino-7-hydroxy- (V; R = NH_2, R′ = H), 4-amino-7-hydroxy- (V; R = H, R′ = NH_2), 4 : 7-dihydroxy-2-methyl (V; R = Me, R′ = OH), 2-amino-4-methyl- (V; R = NH_2, R′ = Me), 4-amino-2 : 7-dihydroxy- (V; R = OH, R′ = NH_2), and 4-amino-7-hydroxy-2-mercapto- (V; R = SH, R′ = NH_2) -6-methylpteridine. Bromination of the first two of these compounds, followed by condensation with *p*-aminobenzoic acid, afforded " 7-hydroxydeamino-pteroic acid " (VI; R = H, R′ = OH) and " 7-hydroxydeoxy-pteroic acid " (VI; R = NH_2, R′ = H), respectively, but attempts to remove the 7-hydroxy-group from these compounds by reduction or by way of the derived 7-halogeno-compounds were unsuccessful.

Seeger *et al.* (*loc. cit.*) showed that the condensation of pyruvic aldehyde with 2 : 4 : 5-triamino-6-hydroxy- and 2 : 4 : 5 : 6-tetra-amino-pyrimidine was sensitive to the reaction conditions, the 7-methyl compound (VII; R = H, R′ = Me) being formed in acid and the 6-methyl compound (VII; R = Me, R′ = H) in sodium sulphite solution. In an attempt to avoid contamination arising from impurities present in commercial pyruvaldehyde, we condensed 2 : 4 : 5-triamino-6-hydroxypyrimidine with hydroxyiminoacetone in saturated aqueous sodium sulphite. Analysis showed the beautifully crystalline product, obtained in excellent yield, to be, not the expected 2-amino-4-hydroxy-6-methylpteridine (VII; R = Me, R′ = H), but a diamino-hydroxy-methylpteridine, clearly (VII; R = Me, R′ = NH_2 or *vice versa*); the yield is much reduced if more dilute sodium sulphite is used and no condensation occurs in glacial acetic acid. Deamination by nitrous acid afforded a trihydroxy-methyl-pteridine; this is not identical with 2 : 4 : 7-trihydroxy-6-methylpteridine, obtained by similar deamination of 2-amino-4 : 7-dihydroxy-6-methylpteridine (VII; R = Me, R′ = OH) prepared by the method of Tschesche *et al.* (*loc. cit.*;

cf. Elion, Hitchings, and Russell, *J. Amer. Chem. Soc.*, 1950, **72**, 78); it is thus clearly 2 : 4 : 6-trihydroxy-7-methylpteridine. The condensation product from 2 : 4 : 5-triamino-6-hydroxypyrimidine and hydroxyiminoacetone is thus clearly 2 : 6-diamino-4-hydroxy-7-methylpteridine (VII; R = NH_2, R′ = Me); the condensation, which fails with 2 : 4-diamino-6-hydroxypyrimidine, possibly involves the initial formation of 2-amino-4-hydroxy-7-methyl-6-hydroxyaminopteridine (VII; R = NH·OH, R′ = Me), which is then reduced.

Modified methods for the preparation of 2 : 4 : 5-triamino- and 2 : 4 : 5-triamino-6-methyl-pyrimidine are described below.

Experimental

Light-absorption data are wave-lengths in mμ for maxima (inflections are italicised) and are followed by ε (in parentheses). All pteridines were dried *in vacuo* at 100—120° before analysis.

Condensation of 2 : 4-*Diamino-6-hydroxy-5-nitrosopyrimidine with Dihydroxyacetone.*—To a solution of the pyrimidine (0·75 g.) in N-sodium hydroxide (10 ml.), dihydroxyacetone dimer was added and the mixture boiled for 2 min. The product, which separated as a brown solid (0·35 g.) on acidification with acetic acid, was oxidised with alkaline permanganate (Forrest and Walker, *J.*, 1949, 2077); the oxidation product was almost entirely 2-amino-4-hydroxypteridine-7-carboxylic acid, identified by the bright green fluorescence of its sodium salt in aqueous solution; only a trace of the blue-fluorescing 6-carboxylic acid was present.

7-*Hydroxypteridines and* 7-*Hydroxypteroic Acids.*—(a) 4-*Hydroxy-compounds.* 4 : 5-Diamino-6-hydroxypyrimidine (2·5 g.), ethyl sodio-oxaloacetate (4·5 g.), and acetic acid (20 ml.) were heated on a boiling water-bath for 1 hr. Water (20 ml.) was then added and the heating continued for a further 30 min. The mustard-yellow solid (3·1 g., 70%) was filtered off and a portion purified by dissolution in hot dilute sodium hydroxide solution and acidification after boiling with charcoal; 4 : 7-*dihydroxy-6-methylpteridine hydrate* (V; R = H, R′ = OH) forms peach-coloured needles, m. p. 345° (decomp.) (Found: C, 43·5; H, 4·15; N, 27·8. $C_7H_6O_2N_4,H_2O$ requires C, 42·85; H, 4·1; N, 28·6%). Light absorption in 0·1N-NaOH: 227 (23,140), 327 (11,200).

Bromine (0·15 ml.) was added dropwise to a solution of this pteridine (0·49 g.) in formic acid (20 ml.), and the mixture kept overnight at room temperature. After removal of hydrogen bromide by partial evaporation under reduced pressure in a stream of nitrogen, *p*-aminobenzoic acid (0·7 g.) in formic acid (10 ml.) was added, and the mixture kept for a further 48 hr. Filtration, followed by dilution with water (to 400 ml.), led to precipitation of the pteroic acid (0·7 g.). This was dissolved in the minimum amount of aqueous ammonia (*d* 0·880), diluted with boiling water to 1200 ml., decolorised with charcoal, and precipitated from the hot solution by acidification (2N-hydrochloric acid) to pH 5. p-N-(4 : 7-*Dihydroxy-6-pteridylmethyl*)*aminobenzoic acid* (" 7-*hydroxy-deamino-pteroic acid* ") (VI; R = H, R′ = OH) (0·2 g., 25%), so obtained was a yellow crystalline solid, m. p. >360° (Found: N, 21·6. $C_{14}H_{11}O_4N_5$ requires N, 22·4%). Light absorption in 0·1N-NaOH: 251 (16,270), 257 (16,270), 280 (19,270), 290 (19,270), 324 (17,210).

(b) 2-*Amino-compounds.* Similar condensation of 2 : 4 : 5-triaminopyrimidine sulphate (1·0 g.) and ethyl sodio-oxaloacetate (1·2 g.) in acetic acid (8 ml.) afforded 2-*amino*-7-*hydroxy-6-methylpteridine* (0·5 g., 62%) (V; R = NH_2, R′ = H), buff-coloured crystals, m. p. >360° (Found: C, 47·6; H, 4·2; N, 39·8. $C_7H_7ON_5$ requires C, 47·5; H, 3·95; N, 39·5%). Light absorption in 0·1N-NaOH: 227 (20,180), 342 (18,580). Bromination and condensation with *p*-aminobenzoic acid, as for the 4-hydroxy-compound, yielded p-N-(2-*amino*-7-*hydroxy*-6-*pteridylmethyl*)*aminobenzoic acid* (" 7-*hydroxy-deoxy-pteroic acid* ") (VI; R = NH_2, R′ = H), as a brown powder, m. p. >360° (Found: N, 25·3. $C_{14}H_{12}O_3N_6$ requires N, 26·9%). Light absorption in 0·1N-NaOH: 228 (27,770), 251 (10,290), 268 (13,730), 280 (13,730), 346 (17,780).

(c) 4-*Amino*-7-*hydroxy*-6-*methylpteridine* (with Maxwell Gordon). Similar condensation of 4 : 5 : 6-triaminopyrimidine sulphate (4·35 g.) with ethyl sodio-oxaloacetate (5·0 g.) in acetic acid (60 ml.) afforded the *pteridine* (V; R = H, R′ = NH_2) (2·5 g., 70%) as pale pink crystals, m. p. >360° (Found: C, 46·7; H, 4·6. $C_7H_7ON_5$ requires C, 47·5; H, 3·95%). Light absorption, at pH 2: 292 (7370), 327 (7530). At pH 7: *282—291*, 336 (7940)).

(d) 4 : 7-*Dihydroxy*-2 : 6-*dimethylpteridine.* 4 : 5-Diamino-6-hydroxy-2-methylpyrimidine sulphate (0·6 g.) and ethyl sodio-oxaloacetate (0·6 g.) were heated at 100° for 2 hr. in acetic acid (7 ml.). Water (7 ml.) was then added and the mixture heated at 100° for a further 30 min. Concentration under reduced pressure and cooling to 0° afforded a yellow solid (0·45 g., 75%),

which was dissolved in 2N-sodium hydroxide (20 ml.); the solution was heated at 100° for 30 min. and acidified with 2N-hydrochloric acid. On cooling in ice, the *pteridine* (V; R = Me, R′ = OH) (0·23 g.) separated (Found: C, 49·4; H, 3·3; N, 29·5. $C_8H_8O_2N_4$ requires C, 50·0; H, 4·2; N, 29·2%). Light absorption in 0·1N-NaOH: 227 (41,180), 328 (13,310).

(e) *2-Amino-7-hydroxy-4: 6-dimethylpteridine.* Condensation of 2 : 4 : 5-triamino-6-methylpyrimidine (0·4 g.) with ethyl sodio-oxaloacetate (0·8 g.) in acetic acid (7 ml.) yielded the *pteridine* (V; R = NH_2, R′ = Me) (0·25 g., 46%) as a cream-coloured powder (Found: C, 50·35; H, 5·0; N, 36·8. $C_8H_9ON_5$ requires C, 50·3; H, 4·7; N, 36·65%). Light absorption in 0·1N-NaOH: 264 (7640), 343 (16,230).

(f) *4-Amino-2: 7-dihydroxy-6-methylpteridine* (with MAXWELL GORDON). Condensation of 4 : 5 : 6-triamino-2-hydroxypyrimidine sulphate (2·15 g.) with ethyl sodio-oxaloacetate (2·5 g.) in acetic acid (30 ml.) afforded the *pteridine* (V; R = OH, R′ = NH_2) (1·9 g., 90%) as an ivory powder (Found: C, 43·8; H, 4·5. $C_7H_7O_2N_5$ requires C, 43·5; H, 3·1%). Light absorption, at pH 2: 272 (15,400), 330 (6030). At pH 9: 272 (12,460), 336 (6830). At pH 13: 254 (8800), 339 (10,400).

(g) *4-Amino-7-hydroxy-2-mercapto-6-methylpteridine* (with MAXWELL GORDON). Condensation of 4 : 5 : 6-triamino-2-mercaptopyrimidine hydrochloride (3·7 g.) with ethyl sodio-oxaloacetate (5·0 g.) in acetic acid (60 ml.) afforded the *pteridine* (V; R = SH, R′ = NH_2) (1·49 g., 40%) (Found: C, 40·35; H, 3·50. $C_7H_7ON_5S$ requires C, 40·2; H, 3·4%). Light absorption at pH 2: 261 (10,300), 349 (14,000).

2 : 6-Diamino-4-hydroxy-7-methylpteridine and its Derivatives.—2 : 4 : 5-Triamino-6-hydroxypyrimidine sulphate (6 g., 0·025 mole) was dissolved by gentle warming in a solution of sodium sulphite (60 g.) in water (200 ml.); the solution was cooled to 30° and hydroxyiminoacetone (2·5 g.) added. A yellow precipitate separated after 15 min. and was collected by filtration (1·5 g.) after the mixture had been kept at room temperature overnight; further crops were collected at intervals over a week. The combined products were washed well with water, ethanol, and ether; the total yield was 3·4 g. (70%). *2 : 6-Diamino-4-hydroxy-7-methylpteridine* (VII; R = NH_2, R′ = Me) crystallised from boiling water in golden leaflets, m. p. >360° (Found: C, 43·8; H, 4·3; N, 43·35. $C_7H_8ON_6$ requires C, 43·75; H, 4·2; N, 43·75%). Light absorption in 0·1N-NaOH: 257 (16,130), 378 (7680).

This pteridine (0·40 g.) was dissolved at 0° in concentrated sulphuric acid (12 ml.) and water (2 ml.) and treated at 0° with sodium nitrite (1·2 g.) in concentrated sulphuric acid (8 ml.). The mixture was kept at room temperature for 10 min. and then poured on ice; the yellow solid, which separated with vigorous evolution of nitrogen, was filtered off after 2 hr. and washed with water, ethanol, and ether. The product (0·20 g.) was suspended in boiling water (70 ml.) and treated dropwise with 2N-sodium hydroxide until a clear solution was obtained; this was boiled with charcoal, filtered, and treated, while boiling, with 2N-hydrochloric acid until cloudy. *2 : 4 : 6-Trihydroxy-7-methylpteridine* separated overnight as bright yellow crystals, m. p. >360° (Found: N, 28·55. $C_7H_6O_3N_4$ requires N, 28·35%). Light absorption in 0·1N-NaOH: 227 (18,430), 280 (7760), 290 (7760), 343 (10,670).

Similar deamination of 2-amino-4 : 7-dihydroxy-6-methylpteridine afforded *2 : 4 : 7-trihydroxy-6-methylpteridine* as a cream-coloured solid, m. p. >300° (Found: N, 27·9. $C_7H_6O_3N_4$ requires N, 28·35%). Light absorption in 0·1N-NaOH: 264 (6210), 330 (12,220).

2 : 4 : 5-Triaminopyrimidine.—Isay's method (*Ber.*, 1906, **39**, 250) was modified as follows (but cf. Albert, Brown, and Cheeseman, *J.*, 1951, 474): 2 : 4-Dichloro-5-nitropyrimidine (3·7 g.) (Whittaker, *J.*, 1951, 1565) was heated for 3 hr. in an autoclave at 100° with ammonia (6 g.) in ethanol (30 ml.). The product was filtered off and recrystallised from boiling water; the yield of 2 : 4-diamino-5-nitropyrimidine, m. p. 355°, was 2·4 g. (82%). This compound (1·3 g.), in ethanol (130 ml.), was hydrogenated at 100°/120 atm. over Raney nickel for 3 hr. Filtration and addition of the theoretical amount of ethanolic sulphuric acid yielded 2 : 4 : 5-triaminopyrimidine sulphate, m. p. 130° (1·2 g., 66%).

2 : 4 : 5-Triamino-6-methylpyrimidine.—The method of Gabriel and Colman (*Ber.*, 1901, **34**, 1234) was modified as follows: 2 : 4-Dihydroxy-6-methyl-5-nitropyrimidine (11·5 g.) (Osten, *Annalen*, 1905, **343**, 137) was refluxed for 3 hr. with phosphorus oxychloride (60 ml.) and dimethylaniline (15 ml.). The resulting solution was concentrated under reduced pressure, poured on ice, and extracted with ether; distillation of the extract, after it had been washed with sodium hydrogen carbonate solution, and dried (Na_2SO_4), afforded 2 : 4-dichloro-6-methyl-5-nitropyrimidine (9·4 g., 67%), b. p. 78°/0·8 mm., m. p. 51°. This was heated in an autoclave at 100° for 3 hr. with ammonia (8 g.) in ethanol (30 ml.). Filtration and recrystallisation from water (800 ml.) afforded 2 : 4-diamino-6-methyl-5-nitropyrimidine (4·5 g., 60%), m. p. 232°,

which was finally hydrogenated in ethanol over Raney nickel at 100°/120 atm. to 2 : 4 : 5-triamino-6-methylpteridine, in 62% yield, m. p. 242° (lit., m. p. 243°).

We thank the Ministry of Education and the Department of Scientific and Industrial Research for Maintenance Allowances (to P. D. L.). We also thank Dr. Maxwell Gordon, in receipt of a grant from the American Cancer Society, who carried out the experiments indicated and also a number of exploratory experiments. The microanalyses were carried out in the microanalytical laboratory of this Department (Mr. F. H. Oliver); the light absorption data were determined by Mrs. A. I. Boston. The work was begun at Birkbeck College, London.

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The Chemistry of Extractives from Hardwoods. Part XXII. The Structure of Diterpenes from* Vouacapoua *Species.*

By F. E. King, D. H. Godson, and T. J. King.

[Reprint Order No. 5926.]

The diterpene ester, methyl vouacapenate, found by Spoelstra (*Rec. Trav. chim.*, 1930, **49**, 226) in *Vouacapoua americana*, has again been isolated from this source and also from the wood of *V. macropetala* where it occurs with the acetate of vouacapenol, the related carbinol.

Vouacapenic acid contains a furan ring, and its selenium-dehydrogenation products are phenanthrene derivatives previously derived from the dodecahydrophenanthrenofuran, vinhaticoic acid (*IA*; R = CO_2H) (King, King, and Neill, *J.*, 1953, 1055; King and King, *ibid.*, p. 4158). Its detailed constitution was ascertained by reduction of the methyl ester $C_{19}H_{27}O{\cdot}CO_2Me$, through vouacapenol and the related aldehyde, to a furano-hydrocarbon $C_{19}H_{27}O{\cdot}Me$, which proved to be identical with the product analogously obtained from methyl vinhaticoate. The two diterpenes are therefore $C_{(4)}$-epimers, the relative optical rotations and hydrolysis rates of their esters indicating that in vouacapenic acid the 1-carboxyl and the 12-methyl group have the *cis*-configuration.

The genus *Vouacapoua* comprises trees of three species found in tropical South America. From the heartwood of *V. americana*, Spoelstra (*Rec. Trav. chim.*, 1930, **49**, 226) isolated a crystalline compound $C_{21}H_{30}O_3$ consisting of the methyl ester of a new diterpene vouacapenic acid. The ester group was found to be difficultly hydrolysable and is presumably a tertiary substituent; the non-carboxylic oxygen atom proved unreactive and was therefore assumed to be etheric. The presence of two double bonds was also demonstrated, but the principal constitutional features of the molecule remained obscure.

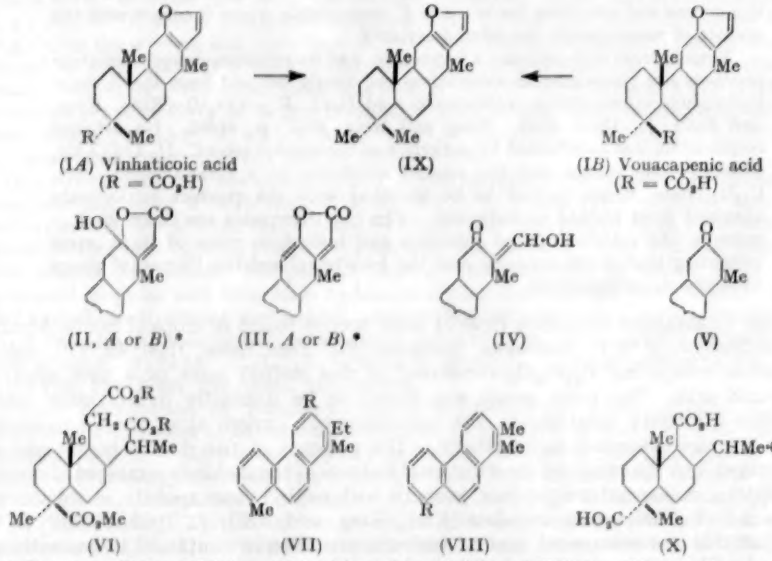
Recently a similar natural product, isomeric with methyl vouacapenate, was discovered in the wood of *Plathymenia reticulata* (King, King, and Neill, *J.*, 1953, 1055). It was shown that this new compound, methyl vinhaticoate, likewise contained two unsaturated bonds and an inert oxygen atom, features which were recognised as the constituents of a furan ring; and, as a result of a more detailed investigation (King and King, *ibid.*, p. 4158), vinhaticoic acid was identified as the dodecahydrophenanthrofuran (*IA*; R = CO_2H). The evident similarity of the two diterpenes has therefore led us to renew the study of methyl vouacapenate which has been isolated in these laboratories not only from *V. americana* but also from a second species hitherto unexamined chemically, *viz.*, *V. macropetala*. We record our appreciation of the generous assistance given by the Conservator of Forests, British Guiana, in securing quantities of these two timbers.

Methyl vouacapenate, comprising 3—3½% of the wood, was isolated by Spoelstra from the syrupy benzene extract of *V. americana*. In the present investigation it was first obtained from *V. macropetala*, boiling light petroleum yielding an oil (6·2%) from which

* Part XXI, *J.*, 1955, 658.

the ester was derived by crystallisation, but the method was wasteful, and in order to recover the remainder the oily residue was distilled. After removal of a portion (0·9%) believed to consist of sesquiterpenes, two fractions were collected, the first being principally methyl vouacapenate, m. p. 103—104°, and the second, of slightly higher boiling point, a new compound, $C_{22}H_{32}O_3$, m. p. 114—115°. Mild alkali hydrolysis of the latter yielded a neutral product, $C_{20}H_{30}O_2$, m. p. 131—132°. The diminished molecular formula corresponded to the loss of an acetyl group, and the compound $C_{22}H_{32}O_3$ was in fact regenerated by acetylating the hydrolysis product of m. p. 131—132°, thereby signifying the alcoholic character of the latter. Owing to the similarity of their boiling points it was more convenient to separate the two crystalline constituents by submitting the combined distillate to vigorous hydrolysis with alkali, the solubility of the resulting vouacapenic acid in the reagent then enabling it to be completely removed from the accompanying alcohol. From the weights of the products thus obtained it was shown that 2·5% of methyl vouacapenate and 1·6% of the acetate $C_{22}H_{32}O_3$ were present in the wood sample.

A consideration of the molecular formula of vouacapenic acid ($C_{20}H_{28}O_3$) and of the alcohol, m. p. 131—132° ($C_{20}H_{30}O_2$), suggested the possibility of a carboxylic acid–primary alcohol relationship. This was confirmed when reduction of the methyl ester with lithium aluminium hydride afforded a product identical in respect of melting point, specific rotation, etc., with the natural alcohol, which was accordingly termed vouacapenol. Later, by treatment with light petroleum, methyl vouacapenate was extracted (by Mr. L. C



* Structures II*A* and III*A* are derived from I*A*, and II*B* and III*B* from I*B*. In the present paper the relative configurations at positions 1 and 12 are denoted by heavy and broken bonds with the 12-methyl group arbitrarily placed in front of the plane of the ring (heavy bond) as in the steroid and triterpene convention; ordinary bonds or absence of bonds denote positions of unknown configuration. In Part XV (*loc. cit.*) the formula for vinhaticoic acid (I*A*) was written on the convention that a 1-carboxyl group written to the left in a formula was *trans* relative to the 12-methyl group and that one written to the right was *cis* (cf. Barton, *Quart. Rev.*, 1949, **3**, 36); unfortunately the formula for vinhatoic acid was reversed in this respect in *Annual Reports*, 1953, **50**, 210.

Manning) from the heartwood of *V. americana* in which it had previously been found by Spoelstra. The presence of cadinene and of free vouacapenic acid has also been demonstrated, but, on the other hand, no trace of vouacapenyl acetate was encountered in this species, nor was any crystalline compound, other than vouacapenic acid, obtained by alkali hydrolysis of the distilled extract.

The absorption spectrum of methyl vouacapenate exhibits a maximum at 222 mμ (log ε 3·72), a value virtually coincident with that of methyl vinhaticoate (220 mμ; log ε 3·88). Both esters are somewhat sensitive to acid reagents and it seemed highly probable therefore that methyl vouacapenate also contained a furanoid system. The extent of their resemblance was further apparent from perphthalic acid oxidation experiments which, as already recorded (King and King, *loc. cit.*), with methyl vinhaticoate gave a derivative (II*A*; R = CO_2Me). The spectrum of this compound which in ethanol has no marked absorption >230 mμ, in 0·2N-ethanolic sodium hydroxide was characterised by $\lambda_{max.}$ at 296 mμ (log ε 3·90); the corresponding oxidation product of methyl vouacapenate has $\lambda_{max.}$ at 294 mμ (log ε 3·73). When heated above their melting points, both compounds form anhydro-derivatives, the product (III*A*; R = CO_2Me) from methyl vinhaticoate having $\lambda_{max.}$ 278 mμ (log ε 4·27), which compares very closely with that of the anhydride from methyl vouacapenate, *i.e.*, $\lambda_{max.}$ 274 mμ (log ε 4·5).

Information as to the nature of the furan ring in methyl vinhaticoate (I; R = CO_2Me) was obtained by ozonolysis of the compound which led first to a β-formyl ketone (IV; R = CO_2Me) and then by further loss of carbon monoxide as formic acid to the ketone (V; R = CO_2Me). Qualitatively similar results were observed with methyl vouacapenate but neither product was obtained crystalline. However, as in the case of methyl vinhaticoate (I*A*; R = CO_2Me), a crystalline acid by-product was isolated, isomeric with the corresponding derivative of (I*A*; R = CO_2Me) to which the structure (VI; R = H) has been attributed.

In order to afford further comparison of the two diterpenes, methyl vouacapenate was subjected to dehydrogenation with selenium. Spoelstra (*loc. cit.*) has observed the formation of two dehydrogenation products without, however, recording details of physical constants or other properties. The two compounds produced in our experiments have been identified as the phenanthrenes (VII; R = H and OH) which are already known from their derivation in a similar manner from methyl vinhaticoate. Furthermore, 1 : 2 : 8-trimethylphenanthrene (VIII; R = Me), which was previously obtained from the unsaturated lactone (III*A*; R = CO_2Me), was likewise formed when the analogous derivative of methyl vouacapenate was aromatised with selenium. It follows therefore that the skeletal structures of the diterpenes are identical and that the two compounds differ merely in the distribution of certain substituents, either in a stereochemical sense or in regard to the relative situation of the 1-methoxycarbonyl * and the quaternary 12-methyl group eliminated during aromatisation, which might occupy inverse positions in methyl vouacapenate. The position of the methoxycarbonyl group was accordingly investigated by the usual method of reduction to the carbinol followed by dehydration, whereupon if the substituent occupies the normal position a molecular rearrangement occurs which leads to the appearance of an ethyl group at position 1 in the subsequent dehydrogenation product (see Part XV, *J.*, 1953, p. 4162, for references). Since dehydration requires the employment of acidic reagents, the furan ring had first to be suitably modified, and this was done by peracid oxidation to a lactone of the type previously described, using vouacapenyl alcohol as starting material. The related anhydro-compound, actually (III*B*; R = CH_2·OH), was then pyrolysed with potassium hydrogen sulphate and the oily product dehydrogenated with selenium. This resulted in the formation of 8-ethyl-1 : 2-dimethylphenanthrene (VIII; R = Et), thus locating the original ester group at position 1 and indicating the purely stereochemical nature of the relation between the two diterpenes. The orientation of the new phenanthrene was deduced by performing a similar sequence of reactions on vinhaticol, the lithium aluminium reduction product of methyl vinhaticoate (I*A*; R = CO_2Me), whereupon the identical hydrocarbon was produced.

Since stereochemical differences among the principal resin acids are generally connected with the relative disposition of their 1-substituents the further examination of methyl vouacapenate (I*B*; R = CO_2Me) was primarily concerned with the configuration of the molecule at this point. Evidence has already been presented (King and King, *loc. cit.*) to show that in the reactions of its methoxycarbonyl group with phenylmagnesium bromide

* In this paper the enumeration, common in diterpenes, is that of phenanthrene starting from the *gem*-disubstituted position.

methyl vinhaticoate closely resembles methyl abietate and is appreciably more reactive than methyl podocarpate. A comparison (see Table) of the rates of hydrolysis of these esters and of methyl vouacapenate demonstrates the striking similarity on the one hand of

Ester hydrolysis in 0·5N-ethanolic potassium hydroxide.

	Time (hr.)	Ester no.		Time (hr.)	Ester no.
Methyl podocarpate	2	0 *	Methyl abietate	2½	73
Methyl vouacapenate ...	4½	2·2 †	Methyl vinhaticoate	2½	109

* Campbell and Todd, *J. Amer. Chem. Soc.*, 1942, **64**, 928. † Spoelstra, *loc. cit.*

methyl vouacapenate and methyl podocarpate, in which latter the methoxycarbonyl and methyl groups are known to be in *cis*-relation, and of methyl vinhaticoate and the abietic ester in which the respective groups are in the *trans*-configuration. From these data it seemed highly probable that the two phenanthrofurans were epimeric, differing solely in the relative positions of their respective 1-methyl and 1-methoxycarbonyl groups. Consequently, by eliminating the asymmetric centre at position 1 it should be possible to convert both diterpenes into a common derivative, and attempts were accordingly made to test this hypothesis by reactions suitable for the conversion of the methoxycarbonyl group into methyl.

The reduction of methyl vinhaticoate to the required furano-hydrocarbon (IX) was effected by means of lithium aluminium hydride in two stages, the first leading to the related alcohol (*IA*; R = CH_2·OH), vinhaticol. The concluding phase, *viz.*, hydrogenolysis of the alcohol toluene-*p*-sulphonate, gave a limited yield (30%) of the desired product (IX) which, however, was not obtained entirely pure (m. p. 74—76°). The more sterically hindered toluene-*p*-sulphonyloxy-group in vouacapenyl toluene-*p*-sulphonate either failed to undergo reaction or, when forcing conditions were applied, regenerated the parent alcohol. The action of lithium aluminium hydride on the methanesulphonyl esters of both vinhaticol and vouacapenol resulted in a nearly quantitative recovery of both alcohols.

The investigation then turned to an alternative route involving aldehydes as intermediates. Catalytic hydrogenation of crude vouacapenoyl chloride, although producing hydrogen chloride (70%), was totally unsuccessful in producing the aldehyde. The acid chloride was converted into the dimethylamide (*IB*; R = CO·NMe_2) and this in turn was treated with lithium aluminium hydride, which might have yielded the required material (*IB*; R = CHO) as in the reduction of phthalobisdimethylamide to phthalaldehyde (Weygand and Teitjen, *Ber.*, 1951, **84**, 625), but only vouacapenol and an unrecognised nitrogenous substance were obtained. The desired aldehyde was first derived from vouacapenol by the Oppenauer procedure, using *p*-benzoquinone–aluminium *tert.*-butoxide, but the amount formed in this way (10%) was unsatisfactory. It was afterwards more readily prepared by oxidising the alcohol with chromic oxide in pyridine (Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422) at room temperature. The crystalline product (*IB*; R = CHO), characterised by an oxime, was reduced by the modified Wolff–Kishner reaction to the furano-hydrocarbon (IX) (65%), m. p. 79°, $[\alpha]_D$ +83°. Oxidation of the isomeric alcohol (*IA*; R = CH_2·OH) similarly gave a crystalline aldehyde, vinhatical, and following the procedure used for vouacapenal, it also yielded the hydrocarbon (IX) (70%), m. p. 79°, $[\alpha]_D$ +84°. The epimeric relation of the two esters is thus finally confirmed, and in view of the hydrolysis data presented in the Table, the relative configurations of vinhaticoic and vouacapenic acids at $C_{(1)}$ may be regarded as analogous respectively to those of abietic acid and podocarpic acid. This conclusion gains further support from molecular rotational data (cf. Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 74), the arithmetical difference between the values of $[M]_D$ for methyl vinhaticoate (+221°) and methyl vouacapenate (+334°), *viz.*, +113°, agreeing very closely with that for methyl 6-methoxydehydroabietate (+243°) and its 1-epimer derived from podocarpic acid (+346°), namely, +103° (Fieser and Fieser, *loc. cit.*). The stereochemistry of the A–C ring junction has not been established, although the foregoing analogies with the abietic–podocarpic acid series suggest that it has the usual *trans*-structure. An attempt

was made to determine the configuration by oxidation of the appropriate compound to the dimethyl*cyclo*hexanetricarboxylic acid obtained from abietic acid (cf. Barton and Schmeidler, *J.*, 1948, 1197), but the action of nitric acid on methyl vinhaticoate failed to effect the desired degradation. The product, a tricarboxylic acid, $C_{17}H_{26}O_{61}$, from which a trimethyl ester was prepared, probably has the constitution (X).

Experimental

Light petroleum used had b. p. 60—80°. Except where otherwise indicated, dried analytical specimens were heated to constant weight at 110° *in vacuo*, and carbon tetrachloride solutions were used for the determination of optical rotations.

Extraction of Vouacapoua macropetala *with Light Petroleum.*—(i) The finely shredded heartwood (2800 g.) was extracted with boiling light petroleum (b. p. 60—80°) for 48 hr., evaporation of the solution leaving a clear brown syrup (174 g., 6·2%). Its solution in light petroleum (400 c.c.) deposited a nearly colourless solid from which methyl vouacapenate (32·5 g.) was obtained by crystallisation from methanol and acetone–methanol as prisms, m. p. 103—104°, $[\alpha]_D$ +101° (*c*, 1·5); light absorption in EtOH, max. at 222 mμ (log ε 3·67) (Found, in a specimen dried at 80° *in vacuo*: C, 76·1; H, 9·1. Calc. for $C_{21}H_{30}O_3$: C, 76·3; H, 9·1%); Spoelstra (*loc. cit.*) has recorded m. p. 105° (corr.), $[\alpha]_D$ +101° (*c*, 3·5). A solution of the ester in acetic anhydride and chloroform became deep crimson on the addition of concentrated sulphuric acid. A mixture of methyl vouacapenate and maleic anhydride in benzene failed to give a crystalline adduct.

Distillation of the residual light petroleum extract (140 g.) afforded two principal fractions, (*a*) b. p. 184—188°/0·2 mm. (31 g.), and (*b*) b. p. 193—197°/0·2 mm. (24 g.), the former when crystallised from methanol yielding methyl vouacapenate (8 g.). Similarly (*b*) gave vouacapenyl acetate (9 g.) (see below), m. p. 114—115°.

(ii) A solution of the light petroleum extract (174 g.) in a minimum of methanol yielded methyl vouacapenate (16·5 g., 0·7%) of m. p. 103—104°. The remainder was distilled and, after removal of the portion of b. p. 130—180°/15 mm. (23·3 g.), the bulk of the residue had b. p. 160—190°/0·1 mm. (118·3 g.). The latter was mixed with a solution of potassium hydroxide (40 g.) in ethylene glycol (70 c.c.), and after expulsion of water at 170—195° the mixture was heated under reflux for 1½ hr. Admixture with water (600 c.c.) precipitated vouacapenol which after thorough washing with boiling water and crystallisation from aqueous methanol had m. p. 130—131° (yield 38·5 g., 1·4%). The solid obtained on acidification of the filtrate and crystallisation from ethanol consisted of vouacapenic acid (51·5 g., 1·8%), m. p. 226—229° (sintering at 214°). The pure acid formed colourless prisms, m. p. 227—230° (sintering at 216°), $[\alpha]_D$ +108° (*c*, 2·5) (Found, in a specimen dried at 130° *in vacuo*: C, 75·9; H, 8·8%; equiv., 327. Calc. for $C_{30}H_{38}O_3$: C, 75·9; H, 8·9%; equiv., 316); Spoelstra recorded m. p. 226—229° (sintering at 215°), $[\alpha]_D$ +107—108° (*c*, 3·5). Vouacapenic acid forms a sodium salt crystallising from water in long silky needles, m. p. >340°.

Vouacapenol (*IB*; R = CH_2·OH).—(i) *Vouacapenyl acetate*, isolated as above by distillation, formed colourless plates (from methanol), m. p. 115°, $[\alpha]_D$ +63°; light absorption in EtOH: max. at 220 mμ (log ε 4·33) [Found, in a dried specimen: C, 76·8; H, 9·3%; *M* (Rast), 325. $C_{32}H_{32}O_3$ requires C, 76·7; H, 9·4%; *M*, 344·5]. The acetate was heated under reflux with 10% alcoholic potassium hydroxide for 1 hr., and the solvent evaporated after the addition of water. The product consisted of *vouacapenol* and crystallised from methanol in prisms, m. p. 130—131°, $[\alpha]_D$ +71° (*c*, 1·8); light absorption in EtOH, max. at 222 mμ (log ε 3·67) (Found, in a dried specimen: C, 79·0; H, 9·9. $C_{30}H_{36}O_3$ requires C, 79·4; H, 10·0%). Acetylation regenerated the acetyl compound, m. p. and mixed m. p. 116°. *Vouacapenyl benzoate*, prepared with benzoyl chloride–pyridine and isolated crystalline by washing with dilute hydrochloric acid, sodium carbonate, and water, separated from ethanol in plates, m. p. 143—145°, after becoming yellow at 110° (Found, in a dried specimen: C, 79·6; H, 8·3. $C_{37}H_{34}O_3$ requires C, 79·8; H, 8·4%).

(ii) Methyl vouacapenate (5 g.), dissolved in ether (100 c.c.), was slowly added to an ethereal solution (50 c.c.) of lithium aluminium hydride (0·4 g.) and, after the initial reaction had subsided, the mixture was refluxed for 45 min. Dilute hydrochloric acid was cautiously added and the product isolated from the ether layer was crystallised from aqueous methanol. Vouacapenol (4 g., 80%) was thus obtained as needles, m. p. alone or mixed with the compound isolated from *V. macropetala*, 131—132°, $[\alpha]_D$ +71° (*c*, 0·8); its acetate had m. p. and mixed m. p. 116°.

Vouacapenol (5·8 g.), toluene-*p*-sulphonyl chloride (5 g.), and dry pyridine (10 c.c.) were heated on a steam-bath for 1 hr. and *vouacapenyl toluene-p-sulphonate* isolated by cooling and the addition of methanol (10 c.c.). Crystallisation from acetone–methanol gave prisms (6·7 g., 65%), m. p. 151° (Found, in a dried specimen: C, 71·0; H, 8·0. $C_{37}H_{56}O_4S$ requires C, 71·0; H, 7·95%). The *methanesulphonate* (85%), similarly prepared and precipitated with water, crystallised from methanol in needles, m. p. 164—165° (Found: C, 66·5; H, 8·5. $C_{21}H_{32}O_4S$ requires C, 66·3; H, 8·5%).

Extraction of V. americana *with Light Petroleum.*—Treatment of the ground wood (4·5 kg.) with boiling light petroleum for 48 hr. and evaporation of the solvent produced a clear brown viscous extract (276 g., 6·14%), and from it a pale yellow aromatic oil (45 g.), b. p. 118—135°/12 mm., was obtained by steam-distillation. Cadinene dihydrochloride was prepared from a portion of the distillate with hydrogen chloride in ether at −20° to −10° (Found: C, 64·9; H, 9·3. Calc. for $C_{15}H_{26}Cl_2$: C, 65·2; H, 9·5%), and from the higher-boiling fraction of the oil, by dehydrogenation with selenium at 200—260° and distillation from sodium, a liquid was prepared which gave a picrate, m. p. 115—116° (cadalene picrate, m. p. 115°) (Found: C, 58·6; H, 4·9. Calc. for $C_{14}H_{16}C_6H_3O_7N_3$: C, 58·1; H, 4·6%). From a solution of the dried non-volatile portion in light petroleum (100 c.c.) diluted with methanol (400 c.c.), crude methyl vouacapenate was obtained which after repeated crystallisation had m. p. 104—105° (yield 60 g.) (Found: C, 75·9; H, 9·2%).

The crystallisation residues (97·6 g.) were distilled and two solid fractions were obtained: (*a*) b. p. 184—195°/0·2 mm. (35·5 g.), and (*b*) b. p. 195—240°/0·2 mm. (25·2 g.). From the former, crude methyl vouacapenate (16 g.), m. p. 98—100°, was obtained which yielded the pure ester, m. p. and mixed m. p. 104—105°, by recrystallisation. From fraction (*b*) vouacapenic acid separated, having m. p. 225—226° (softening at 216°) after crystallisation from methanol or ethyl acetate (yield 4·6 g.) (Found: C, 76·0; H, 8·7. Calc. for $C_{20}H_{28}O_3$: C, 75·9; H, 8·9%), and with diazomethane formed the methyl ester, m. p. 104—105°. A portion (10 g.) of the residue from (*b*), heated with a 20% ethylene glycol solution of potassium hydroxide, gave mainly alkali-soluble material (9 g.), a small unsaponifiable fraction being non-crystalline. The residues from (*a*) were refractionated and methyl vouacapenate was the sole identifiable product.

Oxidation of Methyl Vouacapenate.—(i) *With monoperphthalic acid.* A mixture of the ester (5 g.) in chloroform (50 c.c.) and monoperphthalic acid in ether (100 c.c.) was left at 0° for 50 hr., after which the precipitated phthalic acid was removed and the solution washed with aqueous potassium iodide and sodium thiosulphate. The yellow solid obtained by evaporation was repeatedly washed with boiling water and then kept at 90—100° for 2 hr. Crystallisation from aqueous methanol gave the *lactone* (IIB; R = CO_2Me) (4·2 g.) as colourless plates, m. p. 208—210° (decomp.), which formed rods from ethyl acetate–light petroleum, m. p. 212—214° (decomp.), light absorption in EtOH, max. at 216 mμ (log ε 4·09); in 0·2N-sodium hydroxide in EtOH, max. at 226 and 294 mμ (log ε 3·89 and 3·73) (Found, in a dried specimen: C, 69·7; H, 8·3%; equiv., 360. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·3%; equiv., 362). The lactone dissolved in aqueous sodium carbonate and hydroxide, a sodium salt separating in plates from more concentrated solutions, and was recovered by acidification.

When heated at 230—240° for 15 min. the lactone effervesced and was converted into the *anhydro-derivative* (IIIB; R = CO_2Me) which crystallised from methanol in needles, m. p. 197—198°; light absorption in EtOH, max. at 274 mμ (log ε 4·52) (Found, in a dried specimen: C, 73·1; H, 8·2. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·2%). It was insoluble in aqueous alkali and was recovered on acidification of its solution in cold ethanolic potassium hydroxide.

(ii) *With ozone.* Methyl vouacapenate (7 g.) in ethyl acetate (70 c.c.) at −10° was treated with ozone in excess, and the yellow gum obtained by evaporation of the solvent at 15° was treated with water, first at room temperature for 12 hr. and then for 3 hr. at the b. p. The insoluble product was then dissolved in ether which was extracted with aqueous sodium hydrogen carbonate and with 0·5N-sodium hydroxide. The portion obtained by acidification of the carbonate solution gave *methyl 6-1′-carboxyethyl-5-carboxymethyldecahydro-1 : 10-dimethyl-1-naphthoate* (VI; R = H) which crystallised from ethyl acetate–light petroleum as needles (5 g., 70%), m. p., after drying at 150°, 193—194° [Found, in a dried specimen: C, 64·6; H, 8·5%; *M* (Rast), 403; equiv., 191. $C_{19}H_{30}O_6$ requires C, 64·4; H, 8·5%; *M*, 354; equiv., 177]. Treatment with diazomethane in ether gave, after distillation of the product, b. p. 190—210° (bath-temp.)/0·075 mm., the *trimethyl ester* (VI; R = Me) as prisms from light petroleum, m. p. 63—64° (Found: C, 65·8; H, 8·7; OMe, 23·9. $C_{21}H_{34}O_6$ requires C, 65·9; H, 9·0; 3OMe, 24·3%).

The reddish oil (2 g.) precipitated by acid from the sodium hydroxide-soluble ozonolysis product failed to crystallise and yielded a yellow glass on distillation at 0·1 mm. (bath at 150°).

It gave with alcoholic ferric chloride an intense purple colour. Shaking its solution in chloroform with ammoniacal cupric acetate gave a deep green copper derivative which after evaporation of the solvent crystallised from aqueous ethanol in plates, m. p. 255—258°. Decomposition with 20% sulphuric acid, however, regenerated the presumed dicarbonyl compound in its original non-crystalline condition. A portion (1 g.) was dissolved in 0·5N-sodium hydroxide (30 c.c.) and hydrolysed under reflux. The precipitated brown gum (0·5 g.), which no longer exhibited a ferric reaction, failed to give crystalline derivatives with the usual ketonic reagents.

Ozonolysis with 50% of the theoretical quantity of ozone, and working up with the addition of zinc dust, resulted in an increased proportion of the less acidic material and a considerable recovery of methyl vouacapenate (50—60%).

Selenium Dehydrogenation of the Anhydro-lactone (III*B*; R = CO_2Me).—A mixture of the anhydro-lactone (3 g.) and selenium (6 g.) was heated for 20 hr. at 300—310° and finally at 330—350° for 4 hr. The ether-soluble product was distilled and the portion, b. p. 140—145° (bath-temp.)/0·2 mm., consisted of 1 : 2 : 8-trimethylphenanthrene which crystallised from methanol in plates, m. p. and mixed m. p. 144—145° (Found : C, 93·1; H, 7·4. Calc. for $C_{17}H_{16}$: C, 92·7; H, 7·3%). The picrate had m. p. 167—168° (sintering at 165°) undepressed by a specimen of m. p. 166—168° (recorded m. p. 162—163°), and the trinitrobenzene derivative had m. p. and mixed m. p. 191—192° (Found : C, 63·9; H, 4·1. Calc. for $C_{17}H_{16}.C_6H_3O_6N_3$: C, 63·7; H, 4·4%).

Selenium Dehydrogenation of Methyl Vouacapenate.—The ether-soluble material obtained by heating methyl vouacapenate (5 g.) with selenium (10 g.) at 330—350° for 48 hr. was distilled and the portion of b. p. 120—180° (bath-temp.)/0·07 mm. dissolved in boiling ethanol. The fraction separating at room temperature was recrystallised and formed plates, m. p. 114—115° undepressed when mixed with 2-ethyl-1 : 8-dimethylphenanthrene (VII; R = H) similarly derived from methyl vinhaticoate (I*A*; R = CO_2Me) (King and King, *loc. cit.*) (Found : C, 91·6; H, 7·7. Calc. for $C_{18}H_{18}$: C, 92·3; H, 7·7%); the trinitrobenzene derivative had m. p. and mixed m. p. 167—168°. By evaporating the ethanolic filtrate and crystallising the residue from acetic acid and then light petroleum, 2-ethyl-1 : 8-dimethyl-3-phenanthrol, m. p. 168—169° (decomp.), was obtained identical (mixed m. p.) with a specimen, m. p. 167°, obtained from (I*A*; R = CO_2Me). King and King (*loc. cit.*) found m. p. 164°; the trinitrobenzene derivative had m. p. and mixed m. p. 185—186°.

Vinhaticol (I*A*; R = CH_2·OH).—The reduction of methyl vinhaticoate (5 g.) with lithium aluminium hydride followed the method used for the preparation of vouacapenol. The *product* (I*A*; R = CH_2·OH) (4 g.) crystallised from aqueous methanol in prisms, m. p. 133°, $[\alpha]_D$ +92° (*c*, 1·33) (Found, in a dried specimen : C, 79·7; H, 10·2. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%). With acetic anhydride–sodium acetate the *acetate* was obtained as leafy plates (from methanol), m. p. 81—82° (Found, in a dried specimen : C, 76·8; H, 9·4. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·4%).

*Vinhaticyl toluene-*p*-sulphonate*, prepared in pyridine (yield 60%), formed needles, m. p. 90—91°, from methanol (Found, in a specimen dried at 60° *in vacuo* : C, 71·4; H, 8·1. $C_{27}H_{36}O_4S$ requires C, 71·0; H, 7·95%). The *methanesulphonate*, plates from methanol, had m. p. 117—118° (Found, in a dried specimen : C, 66·0; H, 8·3. $C_{21}H_{32}O_4S$ requires C, 66·3; H, 8·5%).

Perphthalic Acid Oxidation of Vinhaticol and Vouacapenol.—The action of monoperphthalic acid (12 g.) on vinhaticol (I*A*; R = CH_2·OH) (10 g.) in ether (250 c.c.) at 0° for 8 days and then 2—3 days at room temperature caused the deposition of solid which was collected and treated with boiling water (5 × 200 c.c.). The pale yellow crystalline residue (9 g.) had m. p. 230°; a small portion recrystallised from methanol formed colourless prisms of the *product* (II*A*; R = CH_2·OH), m. p. 242—244° (decomp.) (Found : C, 72·2; H, 8·8. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%). Heating the lactone (2 g.) at 240° for 10 min. yielded a resinous product from which the *anhydro-lactone* (III*A*; R = CH_2·OH) (1·7 g.) was obtained as colourless needles, m. p. 180—181°, by crystallisation from methanol (Found : C, 76·1; H, 9·1. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%).

From the oxidation of vouacapenol (10 g.) under comparable conditions a somewhat more soluble product was obtained. It crystallised from methanol yielding the *product* (II*B*; R = CH_2·OH) as plates, m. p. 240—242° (effervescence), solidifying and remelting at 280—282° (Found : C, 71·8; H, 9·0%). The *anhydro-lactone* (III*B*; R = CH_2·OH) formed by heating the oxidation product at 230° for 15 min. was remarkably sparingly soluble, and crystallised from *cyclo*hexanone in needles, m. p. 282—284° (Found, in a specimen dried at 150° *in vacuo* : C, 75·7; H, 8·7%). It dissolved slowly in aqueous-alcoholic potassium hydroxide, the

original compound (II*B*; R = CH_2·OH), m. p. 238—240° (decomp.), being precipitated on acidification.

Conversion of the Anhydro-lactones (III*A*; R = CH_2·OH) *and* (III*B*; R = CH_2·OH) *into 8-Ethyl-1 : 2-dimethylphenanthrene* (VIII; R = Et).—The compound (II*A*; R = CH_2·OH) (6 g.) was first heated at 240° and the resulting crude anhydro-compound intimately mixed with potassium hydrogen sulphate (12 g.). The material was then stirred and heated at 230—240° and, after the initially vigorous gas evolution had ceased (30 min.), the melt was cooled and treated with hot water. The undissolved gum was taken up in ether and distilled, the pale yellow viscous distillate (2·9 g.), b. p. 180—210° (bath-temp.)/0·1 mm., partly crystallising after 2—3 weeks (Found, in a redistilled specimen, b. p. 180—190°/0·1 mm.: C, 80·4; H, 8·6. $C_{20}H_{16}O_3$ requires C, 80·5; H, 8·8%).

The dehydrated mixture (1·52 g.) was dehydrogenated with selenium (4 g.) at 330—350° for 40 hr. and the product isolated with ether and distilled. The portion of b. p. 90—180°/0·07 mm. was dissolved in ethanol (3 c.c.) and added to saturated ethanolic trinitrobenzene (5 c.c.). The solid which separated was collected, dissolved in benzene (10 c.c.), and passed through alumina (40 g.). Elution with light petroleum yielded material crystallising from ethanol finally as plates (10 mg.), m. p. 107—108°, and consisting of *8-ethyl-1 : 2-dimethylphenanthrene* (VIII; R = Et) (Found: C, 92·3; H, 7·8. $C_{18}H_{18}$ requires C, 92·3; H, 7·7%). The *trinitrobenzene derivative*, orange-red needles from ethanol, had m. p. 169—170° (Found: C, 64·8; H, 4·4. $C_{18}H_{18}.C_6H_3O_6N_3$ requires C, 64·4; H, 4·7%).

After preliminary dehydration of the compound (II*B*; R = CH_2·OH) (8·5 g.) derived from vouacapenol to the anhydro-compound (III*B*; R = CH_2·OH), the product was heated with potassium hydrogen sulphate at 240—250° for 45 min. The mixture obtained by distillation as a pale yellow gum (4·2 g.), b. p. 180—210°/0·1 mm., gradually became semi-solid (Found, in a redistilled specimen, b. p. 150—160°/0·05 mm.: C, 80·5; H, 8·4%). Dehydrogenation of a portion (2 g.) under the conditions used for the isomeric material from (III*A*; R = CH_2·OH) yielded 8-ethyl-1 : 2-dimethylphenanthrene, after purification *via* the trinitrobenzene derivative, as plates, m. p. and mixed m. p. 107—108° (Found: C, 92·1; H, 7·6%). The trinitrobenzene derivative, orange-red needles from ethanol, had m. p. and mixed m. p. 169—170° (Found: C, 64·1; H, 4·8%).

NN-*Dimethylvouacapenamide*.—A solution of vouacapenic acid (2·3 g.) in ether (40 c.c.) was treated with thionyl chloride (1 g.) and pyridine (0·2 c.c.) and after 5 hr. the precipitate of pyridine hydrochloride was removed and the liquid quickly washed with 0·2N-sodium hydroxide and dried (Na_2SO_4). Evaporation and heating under reduced pressure at 100° left a light brown gum, supposedly the acid chloride. It was dissolved in xylene (40 c.c.) previously refluxed with Raney nickel and the solution hydrogenated at the b. p. over palladised barium sulphate. Hydrogen chloride (70% of theory) was slowly evolved and evolution ceased only after 50 hr., and evaporation of the filtered solution gave a sparingly-soluble amorphous solid devoid of aldehydic properties.

A specimen of the chloride, prepared as above from 2 g. of acid, was dissolved in aqueous dimethylamine (20 c.c. of 25%) and ethanol (20 c.c.) by warming and after 30 min. at room temperature the solution was diluted with water. The precipitated NN-*dimethylvouacapenamide* crystallised from methanol in plates, m. p. 122—123° (Found, in a dried specimen: C, 76·8; H, 9·5. $C_{22}H_{33}O_2N$ requires C, 76·9; H, 9·7%). Lithium aluminium hydride (0·2 g.), dissolved in ether (10 c.c.), was slowly added to a solution of the amide (0·6 g.) in tetrahydrofuran (5 c.c.), and after 20 hr. the mixture was treated with dilute hydrochloric acid. From the ether vouacapenol (0·1 g.), m. p. and mixed m. p. 130—131°, was isolated; the remaining product, suspended in the aqueous layer, was a nitrogen-containing solid (0·3 g.).

Vouacapenal (I*B*; R = CHO).—(i) The suspension of $CrO_3.2C_5H_5N$ prepared by dissolving chromic anhydride (1 g.) in pyridine (10 c.c.) was mixed with a solution of vouacapenol (1 g.) in pyridine (10 c.c.), and after 1½ hr. at room temperature the dark precipitate was removed and washed with pyridine. The combined pyridine solutions were added to water (300 c.c.) and the mixture shaken with ether (3 × 200 c.c.). When the washed and dried ether extract was isolated it crystallised and separated from methanol finally as colourless plates, m. p. 161—163°, consisting of *vouacapenal* (Found: C, 80·4; H, 9·4. $C_{20}H_{28}O_3$ requires C, 80·0; H, 9·4%). The *oxime*, rods from aqueous ethanol, had m. p. 186—187° (Found: N, 4·5. $C_{20}H_{29}O_3N$ requires N, 4·4%).

(ii) Vouacapenol (0·9 g., 1 mol.), aluminium *tert.*-butoxide (2·8 g., 2 mols.) and *p*-benzoquinone (2·8 g., 10 mols.) were heated under reflux for 15 hr. in purified benzene (30 c.c.). The dark red solid remaining after steam-distillation was repeatedly extracted with ether, and the

ether solution was then washed with 2N-sodium hydroxide until the washings remained colourless. Evaporation of the ether left a red-brown residue which after repeated crystallisation from acetone–methanol (charcoal) formed light brown plates (0·09 g., 10%), m. p. 163—164° alone or mixed with vouacapenal obtained as in (i).

Vinhatical (*1A*; R = CHO).—The oxidation of vinhaticol (2 g.) with chromic anhydride in pyridine as in the preparation of (*1B*; R = CHO) gave the corresponding aldehyde, *vinhatical* (1·3 g., 65%), prisms (from acetone–methanol), m. p. 131—133° (slight decomp.) (Found: C, 80·1; H, 9·3. $C_{20}H_{28}O_2$ requires C, 80·0; H, 9·4%). The *oxime* crystallised from ethanol in prisms, m. p. 205° (Found: C, 76·3; H, 9·1. $C_{20}H_{29}O_2N$ requires C, 76·2; H, 9·3%).

Dodecahydro-1 : 1 : 8 : 12-tetramethylfurano(2′ : 3′-6 : 7)phenanthrene (1X).—(i) The aldehyde (*1A*; R = CHO) (1·3 g.), potassium hydroxide (8 g.), ethylene glycol (80 c.c.), and hydrazine hydrate (2 c.c. of 90%) were heated under reflux for 2 hr., after which the liquid was concentrated to b. p. 190° and treated with more hydrazine hydrate (1 c.c.). Further heating for 2 hr. and evaporation to b. p. 195° was followed by 6 hours' refluxing, the liquid finally being poured into water (600 c.c.). Ether-extraction yielded a brown oil which was distilled, the product, b. p. 110—130° (bath-temp.)/0·1 mm., then solidifying and forming needles, m. p. 77—78°, from ethanol (0·9 g., 70%). Further crystallisation afforded the *furano-hydrocarbon*, m. p. 79°, $[\alpha]_D$ +84° (*c*, 1·13 in $CHCl_3$) (Found: C, 84·2; H, 10·7. $C_{20}H_{30}O$ requires C, 83·9; H, 10·6%).

(ii) A mixture of vouacapenal (1·67 g.) and the corresponding quantities of reagents used in method (i), refluxed first for 1½ hr. and then after evaporation to b. p. 195° for a further 4 hr., gave the identical furano-hydrocarbon (1X), which was isolated as above and formed needles (1 g., 65%), m. p. and mixed m. p. 79°, $[\alpha]_D$ +83° (*c*, 1·13 in $CHCl_3$) (Found: C, 83·8; H, 10·6%).

(iii) A mixture of vinhaticyl toluene-*p*-sulphonate (3 g.) and lithium aluminium hydride (0·6 g.) was heated under reflux in dioxan (60 c.c.) for 20 hr. Dilute hydrochloric acid was then added and the product ether-extracted. Evaporation of the dried solution and distillation gave the hydrofuranophenanthrene as a gum (0·6 g.), b. p. 110—130° (bath-temp.)/0·1 mm., which solidified in contact with ethanol and was finally obtained by recrystallisation as prisms, m. p. 74—76° (Found: C, 83·4; H, 10·2%).

Reduction of the toluene-*p*-sulphonate of vouacapenol with lithium aluminium hydride led either to recovery of the ester or the formation of vouacapenol which was isolated by chromatography on alumina with benzene–light petroleum. The methanesulphonates of both vinhaticol and vouacapenol gave 90% yields of the parent alcohols when reduced with lithium aluminium hydride.

Oxidation of Methyl Vinhaticoate with Nitric Acid.—When methyl vinhaticoate (20 g.) was treated with small portions of a mixture of nitric acid (225 c.c.; *d* 1·4) and the fuming acid (75 c.c.; *d* 1·52), a vigorous reaction occurred. The clear solution was then cautiously heated to 50°, and 1½ hr. after beginning the experiment the temperature was raised to 100° (oil-bath) and 1 hr. later to 130° for a further 2½ hr. The liquid was then evaporated (50—60°/14 mm.) and the gummy residue dissolved in nitric acid (30 c.c.; *d* 1·42) and the solution left to crystallise for 10 days. The deposited solid was recrystallised from ethyl acetate–light petroleum and formed colourless needles, m. p. 220—222° (decomp.) depressed to 213—214° by the dimethyl-*cyclo*hexanetricarboxylic acid, m. p. 218—219°, prepared from abietic acid by oxidation with nitric acid (Barton and Schmeidler, *loc. cit.*) (Found: C, 62·3, 62·5; H, 8·2, 8·2; OMe, nil. $C_{17}H_{26}O_6$ requires C, 62·6; H, 8·0%). The *acid*, believed to be (X), gave with diazomethane a *trimethyl ester*, which after distillation [b. p. 170—190° (bath-temp.)/0·1 mm.] formed rods, m. p. 109—110°, from aqueous methanol (Found: C, 64·9; H, 8·6; OMe, 25·7. $C_{20}H_{32}O_6$ requires C, 65·2; H, 8·8; OMe, 25·2%).

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Simple Analogues of Cortisone. Part IV. Some Benzyl-substituted Glycolloylcyclohexanols.*

By J. D. Billimoria.

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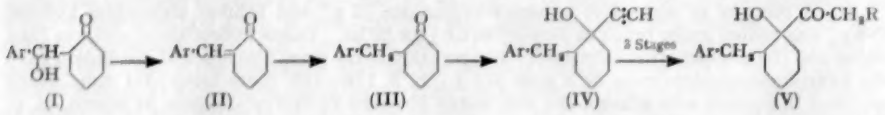
A preparative method for 2-benzyl*cyclo*hexanone and similar compounds substituted in the aromatic nucleus has been devised. Three of these compounds have been converted into the corresponding glycolloyl*cyclo*hexanols or their acetates (V; R = OH or OAc). The stereoisomers were separated at the substituted acetyl*cyclo*hexanol (V; R = H) stage.

Although 2 : 6-dibenzylidene*cyclo*hexanone is well known, the corresponding monobenzylidene compound is obtained only with difficulty. Vorlander and Kunze's method (*Ber.*, 1926, **59**, 2078) was not satisfactory.

In the present method *cyclo*hexanone and benzaldehyde suspended in water and treated with a small quantity of aqueous alkali, under carefully chosen experimental conditions, gave an excellent yield of 2-α-hydroxybenzyl*cyclo*hexanone (I) which, on further treatment with alkali gave a mixture of mono- and di-benzylidene*cyclo*hexanone, the latter predominating. However, the alcohol (I) was smoothly dehydrated by hot aqueous oxalic acid to monobenzylidene*cyclo*hexanone (II). In this manner, *o*-, *m*-, and *p*-methoxy-



and *p*-nitro-benzaldehyde also gave good yields of the respective alcohols (I). Benzaldehyde with *cyclo*pentanone gave mixtures from which only 2 : 5-di-α-hydroxybenzyl*cyclo*pentanone was isolated in small yield but with 2-decalone a mono-α-hydroxybenzyl-2-decalone was obtained in 25% yield.

2-Benzylidene*cyclo*hexanone was hydrogenated over palladium–strontium carbonate to 2-benzyl*cyclo*hexanone, which with sodium acetylide in liquid ammonia gave an inseparable mixture of *cis*- and *trans*-2-benzyl-1-ethynyl*cyclo*hexanol (IV; Ar = Ph); this was hydrated with sulphuric acid in the presence of mercuric sulphate and fractional crystallisation of the resulting mixture yielded crystalline *cis*- and *trans*-1-acetyl-2-benzyl*cyclo*hexanol. The absolute configuration of these compounds is not known; the suffixes A and B used below refer to the higher- and lower-melting ketones and their derivatives respectively.

The ketones (V; Ar = Ph, R = H) were separately brominated in acetic acid to give the two 1-bromoacetyl*cyclo*hexanols (V; R = Br). The bromide A on hydrolysis with alkali in 60% aqueous ethanol gave the 2-benzyl-1-glycolloyl*cyclo*hexanol A as a viscous glass which was characterised as a semicarbazone. However, each isomer of the bromide, on treatment with silver acetate in acetic acid, gave the corresponding crystalline 1-acetoxyacetyl-2-benzyl*cyclo*hexanol (V; R = OAc). All compounds of the A series were distinct from those of the B series and mixed melting points were depressed.

2-(2-Methoxy-α-hydroxybenzyl)*cyclo*hexanone (I, Ar = *o*-hydroxyphenyl) was successfully converted into 2-2′-methoxybenzyl*cyclo*hexanone and thence into 1-ethynyl-2-2′-methoxybenzyl*cyclo*hexanol. Hydration of the last compound yielded no ketonic material.

In similar experiments the 1-acetyl-2-4′-methoxybenzyl*cyclo*hexanol (V; Ar = *p*-hydroxyphenyl, R = H) was obtained from the keto-alcohol (I) and separated into two isomers. Isomer A was crystalline and after bromination with dioxan dibromide in ether and hydrolysis of the bromide with Deacidite F.F. (cf. Part III, *loc. cit.*) gave 1-glycolloyl-2-4′-methoxybenzyl*cyclo*hexanol (V; R = OH). Isomer B (V; R = H) was liquid, probably contained some isomer A, and was not further pursued.

* Part III, *J.*, 1954, 3257.

The three keto-alcohols, 1-acetoxyacetyl-2-benzyl*cyclo*hexanol A and B and 1-glycolloyl-2-4′-methoxybenzyl*cyclo*hexanol A, were found to have no cortisone-like activity when assayed by the mouse liver-glycogen (Part III, *loc. cit.*) and the cold-stress method.

Experimental

The microanalyses were carried out in the Microanalytical Laboratory, Organic Chemistry Department, Imperial College (Mr. F. H. Oliver).

2-α-*Hydroxybenzyl*cyclo*hexanone*.—*cyclo*Hexanone (300 g.) and benzaldehyde (212 g.) were suspended in water (6 l.), and sodium hydroxide (21 g.) in water (1 l.) was added. The mixture was stirred at room temp. for 4 hr., light petroleum (b. p. 40—60°) (500 c.c.) added, and the precipitated keto-alcohol (450 g.) collected and washed with cold light petroleum (b. p. 40—60°) (1·5 l.). A portion of the 2-α-hydroxybenzyl*cyclo*hexanone was crystallised from aqueous acetone, forming colourless needles, m. p. 99—100° (Vorlander and Kunze, *loc. cit.*, give m. p. 101—102°) (Found: C, 76·5; H, 7·9. Calc. for $C_{13}H_{16}O_2$: C, 76·5; H, 7·8%).

2-*Benzylidene*cyclo*hexanone*.—The above compound (crude, 400 g.) was heated under reflux for 2 hr. with water (1500 c.c.) and oxalic acid (400 g.). The mixture was cooled and extracted with ether, and the organic layer repeatedly washed with sodium hydrogen carbonate solution and dried (Na_2SO_4). Distillation in a high vacuum gave an oil (337 g.) which crystallised (m. p. 52—53°). Recrystallisation from light petroleum (b. p. 40—60°) gave pale yellow needles of 2-benzylidene*cyclo*hexanone, m. p. 53—54° (Found: C, 83·8; H, 7·5. Calc. for $C_{13}H_{14}O$: C, 83·9; H, 7·5%).

2-*Benzyl*cyclo*hexanone*.—The above compound (300 g.) in ethanol (1 l.) was hydrogenated over 2% palladium–strontium carbonate (25 g.) at 100 atm. (initial). Distillation gave colourless 2-*benzyl*cyclo*hexanone* (300 g.), b. p. 142°/1 mm., n_D^{18} 1·5356 (Found: C, 83·0; H, 8·8. $C_{13}H_{16}O$ requires C, 82·9; H, 8·5%).

2-*Benzyl*-1-*ethynyl*cyclo*hexanol*.—Sodium acetylide (from sodium, 33 g.) was formed in liquid ammonia (3 l.) by using Nieuwland's catalyst (Vaughan, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120), and 2-benzyl*cyclo*hexanone (188 g.) in dry ether (200 c.c.) was run in during 1·5 hr. whilst a rapid stream of acetylene was passed through the solution. The stream of acetylene was continued for 2 hr. after complete addition of the ketone, and the mixture stirred overnight. Working up in the usual manner afforded 2-*benzyl*-1-*ethynyl*cyclo*hexanol* (180 g.), b. p. 152°/1 mm. (bath-temp. 170°), n_D^{21} 1·5431 (Found: C, 84·0; H, 8·3. $C_{15}H_{18}O$ requires C, 84·1; H, 8·4%). The liquid was a mixture of *cis*- and *trans*-isomers and could not be separated by fractionation.

1-*Acetyl*-2-*benzyl*cyclo*hexanol*.—2-Benzyl-1-ethynyl*cyclo*hexanol (200 g.) was run into a solution of mercuric sulphate (110 g.) in sulphuric acid (300 c.c.) and water (2500 c.c.) during 1 hr. at 30—40°. Stirring was continued until the precipitated complex again became liquid (3—4 hr.). Light petroleum (b. p. 80—100°) (1 l.) was added and the mixture heated under reflux for 2 hr. The mixture was cooled and the organic layer separated. After filtering, the aqueous layer was extracted with ether (2 × 500 c.c.), and the precipitate washed under suction with ether (500 c.c.). The combined organic solvents were evaporated in a vacuum and the mixture of *cis*- and *trans*-ketone was obtained as a crystalline mass (180 g.), m. p. 45—75°.

These crystals (435 g.; from two experiments) were dissolved in a mixture of light petroleums (b. p. 40—60°, 1 l.; b. p. 80—100°, 400 c.c.) and cooled to room temperature. After 24 hr. crop (I) (123 g.; m. p. 82—84°) was separated. Subsequent concentration to half-bulk and cooling gave crop (II) (61 g.; m. p. 60—65°); further cooling to 0° gave crop (III) (31 g.; m. p. 63—65°); further evaporation gave crop (IV) (m. p. 45—50°; 215 g.). A portion of crop (I) after a number of crystallisations from light petroleum (b. p. 80—100°) gave a compound, m. p. 86—87°, and similar crystallisation of crop (IV) from light petroleum (b. p. 40—60°) gave a compound m. p. 55—56°. Crops (I)—(III) were combined, dissolved in light petroleum (b. p. 80—100°), and seeded with the higher-melting ketone, yielding 1-*acetyl*-2-*benzyl*cyclo*hexanol A* (190 g.), m. p. 86—87° unaltered on further crystallisation. Seeding of a solution of crop (IV) gave 1-*acetyl*-2-*benzyl*cyclo*hexanol B* (151 g.), m. p. 55—56°. A mixed m. p. was 46° (not sharp) (Isomer A, found: C, 77·8; H, 8·8. Isomer B, found: C, 77·6; H, 8·7. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·7%). The *semicarbazone A*, prepared in aqueous-alcoholic sodium acetate, separated from ethanol in needles, m. p. 236—237°, and the *semicarbazone B* from ethanol in needles, m. p. 214° (mixed m. p. 200—205°) (Isomer A, found: C, 66·8; H, 8·2; N, 14·5. Isomer B, found: C, 66·7; H, 8·2; N, 14·5. $C_{16}H_{23}O_2N_3$ requires C, 66·8; H, 8·0; N, 14·5%).

2-*Benzyl*-1-*bromoacetyl*cyclo*hexanol*.—1-Acetyl-2-benzyl*cyclo*hexanol A (23·2 g.) was dissolved in chloroform (200 c.c.), and bromine (16 g.) in chloroform (100 c.c.) containing hydrogen bromide in acetic acid (0·5 c.c., 50% by weight) was added. After the colour of bromine had disappeared (15 min.), the mixture was washed with water (2 × 50 c.c.), the aqueous layers were extracted with chloroform (2 × 20 c.c.), and the chloroform layers combined, dried (Na_2SO_4), and evaporated *in vacuo*. The residue on crystallisation from light petroleum (b. p. 80—100°) gave colourless needles of 2-*benzyl*-1-*bromoacetyl*cyclo*hexanol A* (18 g.), m. p. 114—115° (Found: C, 57·8; H, 6·3; Br, 25·9. $C_{15}H_{19}O_2Br$ requires C, 58·0; H, 6·2; Br, 25·7%).

The ketone B (23·2 g.) and bromine (16 g.) in the same manner gave the *bromide B* (15·5 g.), crystallising from light petroleum (b. p. 80—100°) in needles, m. p. 105° (Found: C, 57·7; H, 6·4; Br, 25·6%).

1-*Acetoxyacetyl*-2-*benzyl*cyclo*hexanol*.—The bromide A (48 g.) in acetic acid (500 c.c.) was refluxed under nitrogen with silver acetate (100 g.) for 24 hr. The solution was filtered, the silver halide was washed thoroughly with ether, and the combined filtrates were evaporated *in vacuo*. The residue was dissolved in ether and washed with aqueous sodium hydrogen carbonate. Removal of the solvent followed by distillation in a high vacuum yielded a pale yellow glass (20 g.), b. p. 130—140°/10^{-5} mm. (bath temp. 160—165°). On crystallisation from light petroleum (b. p. 80—100°), colourless needles of 1-*acetoxyacetyl*-2-*benzyl*cyclo*hexanol A* (12 g.), m. p. 86°, were obtained (Found: C, 70·3; H, 7·8. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%).

The bromide B (10 g.) similarly gave the *acetoxy-ketol B* (1·2 g.) which crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 69—70° (Found: C, 69·9; H, 7·7%). The *semicarbazone B* separated from ethanol in needles, m. p. 182—183° (Found: C, 62·3; H, 7·4; N, 12·3. $C_{18}H_{25}O_4N_3$ requires C, 62·2; H, 7·2; N, 12·1%).

2-*Benzyl*-1-*glycolloyl*cyclo*hexanol A*.—2-Benzyl-1-bromoacetyl*cyclo*hexanol A (11·8 g.) in aqueous ethanol (100 c.c.; 60% w/v) was treated with aqueous-ethanolic sodium hydroxide (2 g. in 50 c.c. of 60% ethanol w/v) in nitrogen. Each portion of alkali was allowed to be neutralised (phenolphthalein) before subsequent additions were made. Evaporation *in vacuo* followed by extraction with ether and removal of solvent left a colourless glass (4 g.) which gave a *semicarbazone*, needles (from ethanol), m. p. 195—198° (decomp.) (Found: C, 62·8; H, 7·7; N, 13·4. $C_{16}H_{23}O_3N_3$ requires C, 63·0; H, 7·6; N, 13·7%).

2-(2-*Methoxy*-α-*hydroxybenzyl*)cyclo*hexanone*.—*o*-Methoxybenzaldehyde (68 g.) was mechanically shaken with *cyclo*hexanone (69 g.) and sodium hydroxide (6 g.) in water (2 l.). After 3 hr. the precipitate (116 g.) was collected and a portion on crystallisation from aqueous ethanol gave the *keto-alcohol* in colourless plates, m. p. 113—114° (Found: C, 72·0; H, 7·7. $C_{14}H_{18}O_3$ requires C, 72·0; H, 7·8%).

2-2′-*Methoxybenzylidene*cyclo*hexanone*.—The above compound (500 g.), refluxed with oxalic acid (600 g.) and water (2 l.) for 2½ hr., gave the required *benzylidene compound* (430 g.) which separated from ether in large yellow rods, m. p. 79—80° (Found: C, 78·0; H, 7·4. $C_{14}H_{16}O_2$ requires C, 78·0; H, 7·4%).

2-2′-*Methoxybenzyl*cyclo*hexanone*.—2-2′-Methoxybenzylidene*cyclo*hexanone (400 g.) in ethanol (1 l.), hydrogenated as above, afforded the saturated *compound* (400 g.), b. p. 102—106°/0·1 mm., $n_D^{21\cdot5}$ 1·5399 (Found: C, 77·0; H, 8·5. $C_{14}H_{18}O_2$ requires C, 77·1; H, 8·3%) [*semicarbazone*, needles (from ethanol), m. p. 201° (Found: C, 65·5; H, 7·8; N, 15·4. $C_{15}H_{21}O_2N_3$ requires C, 65·5; H, 7·8; N, 15·4%)].

1-*Ethynyl*-2-2′-*methoxybenzyl*cyclo*hexanol*.—2-2′-Methoxybenzyl*cyclo*hexanone (300 g.) was treated with sodium acetylide (from sodium, 48 g.) in liquid ammonia (5 l.). After distillation the acetylenic *alcohol* was obtained as a pale yellow liquid, b. p. 145°/2 mm., $n_D^{24\cdot5}$ 1·5468 (Found: C, 78·1; H, 7·9. $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%).

2-(4′-*Methoxy*-α-*hydroxybenzyl*)cyclo*hexanone*.—*p*-Methoxybenzaldehyde (272 g.) and *cyclo*hexanone (245 g.) were stirred with sodium hydroxide (6 g.) in water (2 l.) for 4 hr. The mixture was added to light petroleum (b. p. 40°) and set aside at 0° for 12 hr. The precipitate was filtered off, rapidly dissolved in acetone (1 l., preheated to its b. p.), and allowed to cool to 0°. (The *compound* is thermolabile when heated with the solvent.) The colourless plates (390 g.), m. p. 117—119°, were filtered off. A specimen recrystallised from hot acetone gave plates, m. p. 119—120° (Found: C, 72·0; H, 7·8. $C_{14}H_{18}O_3$ requires C, 72·0; H, 7·7%).

2-4′-*Methoxybenzylidene*cyclo*hexanone*.—This compound was obtained in 90% yield from the above product by treatment with aqueous oxalic acid as previously described. After distillation in a high vacuum it separated from *n*-hexane in yellow needles, m. p. 71—73° (Found: C, 77·8; H, 7·4. Calc. for $C_{14}H_{16}O_2$: C, 77·8; H, 7·4%).

2-4′-*Methoxybenzyl*cyclo*hexanone*.—Hydrogenation of the above benzylidene compound (200 g.) in methanol as above and distillation gave 2-4′-*methoxybenzyl*cyclo*hexanone* (195 g.), b. p. 138°/0·5 mm., n_D^{21} 1·5381 (Found: C, 65·5; H, 7·9; N, 15·6. $C_{15}H_{21}O_2N_3$ requires C, 65·5; H, 7·6; N, 15·2%).

1-*Ethynyl*-2-4′-*methoxybenzyl*cyclo*hexanol*.—2-4′-Methoxybenzyl*cyclo*hexanone (151 g.) was treated with lithium acetylide (from lithium, 7 g.) in liquid ammonia (2·5 l.). The acetylenic *alcohol* (122 g.) was obtained by distillation as a colourless liquid, b. p. 138—140°/10^{-6} mm., n_D^{18} 1·5455 (Found: C, 78·3; H, 7·9; $C_{16}H_{20}O_2$ requires C, 78·7; H, 8·2%).

1-*Acetyl*-2-4′-*methoxybenzyl*cyclo*hexanol*.—The above alcohol (100 g.) in methanol (270 c.c.) and water (70 c.c.) was refluxed under stirring with "Zeokarb 225" (mesh below 50 μ; 100 g.; previously treated with a solution of 20% mercuric sulphate in 2N-sulphuric acid). The test for an acetylenic alcohol (liberation of acid by aqueous silver nitrate) was weak after 6 hr. The resin was then filtered off and distillation of the filtrate gave 1-acetyl-2-4′-methoxybenzyl-*cyclo*hexanol (mixed isomers) as a viscous liquid (70 g.), b. p. 132°/10^{-4} mm. The mixture was converted into the semicarbazone, which separated from ethanol in needles, m. p. 194—200° (Found: C, 64·1; H, 7·9; N, 13·4. Calc. for $C_{17}H_{25}O_2N_3$: C, 64·0; H, 7·8; N, 13·1%). The semicarbazone (34 g.) on treatment with acid gave the ketone (25 g.) which after distillation was kept at 0° for several weeks. One pure isomer crystallised and recrystallisation from light petroleum (b. p. 40—60°) gave 1-*acetyl*-2-4′-*methoxybenzyl*cyclo*hexanol A* (13 g.), m. p. 74·5° (Found: C, 73·3; H, 8·4. $C_{16}H_{22}O_3$ requires C, 73·5; H, 8·4%). The liquid fraction gave the impure B-isomer, b. p. 136°/10^{-6} mm. (Found: C, 73·1; H, 8·6%).

1-*Glycolloyl*-2-4′-*methoxybenzyl*cyclo*hexanone A*.—The above ketone (solid isomer, 6·5 g.) was dissolved in ether (100 c.c.), and dioxan dibromide (6·1 g.) in ether (50 c.c.) was added. The solution was irradiated with a 250-w lamp until colourless, then washed with water and evaporated, to yield the crude bromide (5 g.). This oil, in methanol (200 c.c.) and water (80 c.c.), was heated on the water-bath for 2 hr. with "Deacidite F.F." (25 g.) under nitrogen. After isolation in the usual manner 1-glycolloyl-2-4′-methoxybenzyl*cyclo*hexanol A (1·3 g.) separated from ether–light petroleum (b. p. 40—60°) in cubes, m. p. 64—67° (Found: C, 69·9; H, 8·1. $C_{16}H_{22}O_4$ requires C, 69·5; H, 8·0%).

2-(4-*Nitro*-α-*hydroxybenzyl*)cyclo*hexanone*.—The *compound* obtained in 90% yield by condensation of *p*-nitrobenzaldehyde and *cyclo*hexanone under conditions already described separated from methanol in colourless needles, m. p. 150—151° (Found: C, 62·2; H, 6·1; N, 5·8. $C_{13}H_{15}O_4N$ requires C, 63·0; H, 6·1; N, 5·6%).

2 : 5-*Di*-(α-*hydroxybenzyl*)cyclo*pentanone*.—The *compound* (10% yield) separated from ethanol in needles, m. p. 144—145° (Found: C, 77·1; H, 6·9. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%).

x-(α-*Hydroxybenzyl*)-2-*decalone* separated from methanol in colourless needles, m. p. 116—117° (Found: C, 79·2; H, 8·7. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·5%).

Biological Assay.—The cold-stress test, as developed by D'Arcy (*J. Pharm.*, 1954, **6**, 65) and Buttle, D'Arcy, and Howard (*J. Physiol.*, 1954, **123**, 5P), was applied to bilaterally adrenalectomised mice of 12—15 g. Groups of 9—11 mice were injected with two equal doses of test material dissolved in arachis oil, one dose on the evening of the first and one on the morning of the second postoperative day. A simultaneously run control group was injected with arachis oil only. An hour after the final injection, the mice were stressed at 5°, being observed at half hourly intervals until all were dead.

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Experiments on the Synthesis of Santonin. Part IV. The Preparation of the Lactone of 1 : 2 : 3 : 4 : 7 : 10-Hexahydro-1-hydroxy-8 : 10-dimethyl-7-oxo-2-naphthylacetic Acid (Norsantonin) and of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-Octahydro-1-hydroxy-10-methyl-7-oxo-2-naphthylacetic Acid.*

By F. D. Gunstone and A. P. Tulloch.

[Reprint Order No. 5966.]

The two compounds named in the title (IV; R = Me, R′ = H) and (VIII; R = H) respectively, both closely related to santonin, have been prepared.

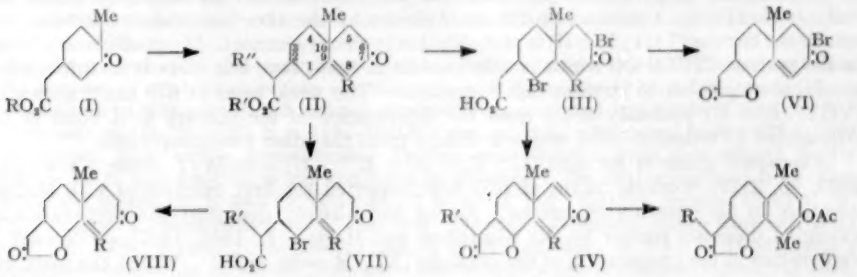
In earlier papers in this series we described compounds required in attempts to synthesise santonin (IV; R = R′ = Me) but whilst this work was in progress Japanese workers reported the synthesis of santonin and some of its stereoisomers (Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *Proc. Jap. Acad.*, 1952, **28**, 425; 1953, **29**, 113; 1954, **30**, 116, 119; *J. Amer. Chem. Soc.*, 1953, **75**, 2567; Matsui, Toki, Kitamura, Suziki, and Humura, *Bull. Chem. Soc. Japan*, 1954, **27**, 7). Accordingly we transferred our attention to the synthesis of compounds closely related to santonin and we now report the synthesis of two lactones (IV; R = Me, R′ = H) and (VIII; R = H); the first differs from santonin only in the absence of the side-ring (α) methyl group whilst the latter is without the 8- and the α-methyl group and is hydrogenated at the 5 : 6-position.

Preparation of Norsantonin (IV; R = Me, R′ = H).—Methyl 4-methyl-3-oxo*cyclo*hexyl acetate (I; R = Me) was readily obtained from ethyl 1-methyl-2-oxo*cyclo*hex-3-ene-1-carboxylate (Mukherjee, *J. Indian Chem. Soc.*, 1948, **25**, 155; cf. Gunstone and Tulloch, *J. Appl. Chem.*, 1954, **4**, 291) by Michael condensation with diethyl malonate followed by hydrolysis, decarboxylation, and methylation. The corresponding acid (I; R = H) should exist in two racemic forms but the product appeared to be almost entirely one isomer which was easily isolated; the alternative form was not obtained pure. Condensed with 1-diethylaminopentan-3-one methiodide this keto-ester (I; R = Me) afforded methyl 1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-octahydro-8 : 10-dimethyl-7-oxo-2-naphthylacetate (II; R = R′ = Me, R″ = H) (cf. Gunstone and Tulloch, *loc. cit.* and references there cited) and gave the corresponding acid when hydrolysed. With bromine in ether–acetic acid in the presence of a little hydrogen bromide this gave a dibromo-acid assigned the structure (III; R = Me) on account of many analogous reactions in the steroid series (see, *e.g.*, Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534) and of its subsequent reactions. This result differs slightly from that of Abe *et al.* (*loc. cit.*, 1953) who, working with trimethyl compounds (II; R = R″ = Me, R′ = H), obtained directly a monobromo-lactone; on the other hand, Matsui *et al.* (*loc. cit.*), using the same acid, isolated like us the dibromo-acid. When heated with collidine under strictly controlled conditions this dibromo-acid (III; R = Me) was converted into the lactone (IV; R = Me, R′ = H) which is a norsantonin. That the compound has this structure follows from the facts that it is neutral, that its ultra-violet absorption curve shows a single peak at 243 mμ characteristic of dienones of this type (for references see Gunstone and Heggie, *J.*, 1952, 1437), and that, when submitted to the conditions of a dienone-phenol rearrangement, it affords the acetylated phenol (V; R = H) with ultra-violet spectrum almost identical with that of the analogous product prepared from santonin (see p. 1134). Additional evidence follows from the infra-red spectra which are discussed below.

The acid (II; R = Me, R′ = R″ = H) with *N*-bromosuccinimide gave a monobromo-acid (VII; R = Me, R′ = H) in good yield but this afforded only a small quantity of impure lactone when treated with sodium ethoxide. We have shown in our earlier papers

* Part III, *J. Appl. Chem.*, 1954, **4**, 291.

that under these conditions bromination occurs in the 1-position and Abe *et al.*, working with the trimethyl acid, obtained the lactone directly by this means.



Preparation of the Lactone (VIII; R = H).—The experiments now to be described were carried out in an attempt to prepare the santonin analogue (IV; R = R′ = H); this however was not achieved and only the dihydro-compound (VIII; R = H) could be obtained. Methyl 4-methyl-3-oxo*cyclo*hexyl acetate (I; R = Me) condensed with 1-diethylaminobutan-2-one methiodide to give the octalone (II; R = R″ = H, R′ = Me) which served as the starting point for attempts to prepare the lactone (IV; R = R′ = H).

The method used for the conversion of the dimethyl acid (II; R = Me, R′ = R″ = H) into the lactone (IV; R = Me, R′ = H) was applied to the monomethyl acid (II; R = R′ = R″ = H) without success. Hydrolysis of the ester (II; R = R″ = H, R′ = Me) gave the acid (II; R = R′ = R″ = H), one isomeric form of which was readily obtained. Bromination then afforded the dibromo-acid but dehydrobromination yielded only a small quantity of a bromo-lactone, probably (VI). Attempts to remove the second bromine atom failed.

Monobromination (*N*-bromosuccinimide) of the acid (II; R = R′ = R″ = H) gave the bromo-acid (VII; R = R′ = H) which, without purification, was lactonised in good yield. We have not been able to introduce an additional double bond into this compound which would convert it into (IV; R = R′ = H). The structure assigned to the lactone (VIII; R = H) is in accord with the ultra-violet and infra-red spectra.

Infra-red Spectra.—The infra-red spectra of natural santonin and of the two related lactones now synthesised have been measured and compared (4% solution in $CHCl_3$; model 13 Perkin-Elmer infra-red spectrometer, fitted with a sodium chloride prism) (see

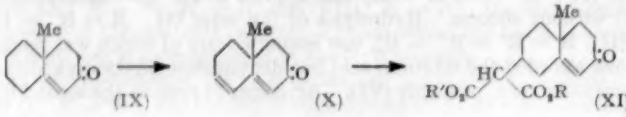
Santonin (IV; R = R′ = Me)			Norsantonin (IV; R = Me, R′ = H)			Lactone (VIII; R = H)		
3020 (m)	1780 (s)	1608 (m)	3020 (m)	1780 (s)	1170 (ms)	3020 (m)	1780 (s)	1170 (ms)
2920 (m)	1664 (s)	990 (ms)	2920 (m)	1660 (s)	835 (m)	2920 (m)	1666 (s)	875 (w)
2850 (sh.w)	1636 (ms)	835 (m)	2850 (w)	1628 (ms)		2850 (w)	1636 (sh.w)	

Table, where figures are cm.$^{-1}$, s = strong, m = medium, w = weak, and sh. = shoulder). As expected, all show comparable bands at 3020, 2920, and 2850 cm.$^{-1}$, due to C–H stretching in :CH and ·CH_2, a strong band at 1780 cm.$^{-1}$ characteristic of the C:O stretching in a five-membered lactone, and a band at 1660—1666 cm.$^{-1}$ due to the C:O stretching in the ·C:C·C:O system. The bands in the 1608—1636-cm.$^{-1}$ region are considered to arise from the C:C stretching of the ·C:C·C:O system; in the lactone (VIII; R = H) there is only one such ethylenic bond and absorption is accordingly weak, in the norsantonin (IV; R = Me, R′ = H) there are two such ethylenic bonds leading to stronger absorption which appears as a twin peak in santonin itself; the non-separation of the peaks in the norsantonin spectrum, which is not unusual, may be due to steric factors. The two synthetic compounds have a fairly intense band at 1170 cm.$^{-1}$ replaced in santonin by one at 990 cm.$^{-1}$: these peaks are considered to be due to the C–O stretching of the lactone which is reported to be variable within the range 1300—1000 cm.$^{-1}$ (Bellamy, "Infra-Red Spectra of Complex Molecules," Methuen, London, 1954). The differences

observed here may be related to the fact that santonin is believed to have its lactone ring *trans*-fused (Barton, *J. Org. Chem.*, 1950, **15**, 466) whilst our synthetic compounds probably have the lactone ring *cis*-fused (Abe *et al.*, *loc. cit.*, 1954; Cocker and McMurry, *Chem. and Ind.*, 1954, 1199). The band at 835 cm.$^{-1}$ shown by the two diunsaturated ketones but not by the lactone (VIII; R = H) is probably due to the *cis*-olefinic C–H out-of-plane bending in the system ·CH:CH·CO which is only present in these two, but there is no information available at present to confirm this suggestion. The weak band at 875 cm.$^{-1}$ shown by (VIII; R = H) probably arises from the deformation of the solitary C–H bond in the conjugated 1 : 9-double bond which is absent from the other two compounds.

Alternative Route to the Acid (II; R = R′ = R″ = H).—Ralls (*J. Amer. Chem. Soc.*, 1953, **75**, 2123), working in the steroid field, reported the first example of 1 : 6 Michael addition to an unsaturated ketone. As we had already described the preparation of extended dienones similar to (X) (Gunstone and Heggie, *J.*, 1952, 1437) we decided to exploit this in the preparation of the octalone (XI; R = R′ = Et). Whilst the work was in progress other workers applied this reaction to the preparation of homologues of (XI) (Matsui, Toki, Kitamura, Suziki, and Hamura, *Bull. Chem. Soc. Japan*, 1954, **27**, 7; Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *Proc. Jap. Acad.*, 1954, **30**, 116; McQuillin, *Chem. and Ind.*, 1954, 311).

The octalone (IX), prepared by the method previously described (du Feu, McQuillin, and Robinson, *J.*, 1937, **53**; Gunstone and Heggie, *loc. cit.*) but with sodium methoxide in place of sodamide, was brominated with *N*-bromosuccinimide and dehydrobrominated with collidine. The product was mainly the dienone (X) contaminated with a little unchanged



starting material; this dienone has been prepared before (Yanagita and Tahara, *J. Org. Chem.*, 1953, **18**, 792) but on a small scale and in low yield. Michael addition, effected with one equivalent of sodium ethoxide, gave the substituted octalone (XI; R = R′ = Et) which was readily hydrolysed to the corresponding malonic acid (XI; R = R′ = H). Decarboxylation then gave the monobasic acid (II) (R = R′ = R″ = H) but, whereas the compound previously obtained melted at 113—115°, this sample had m. p. 85—88° and is probably an isomer. Unfortunately we have been unable to prepare an analytically pure sample of this material despite several attempts and the fact that compounds prepared from it gave satisfactory analyses. Abe *et al.* (*loc. cit.*, 1954) obtained different isomers when preparing the homologue (II; R = R″ = Me, R′ = H) by these two routes. The malonic ester (XI; R = R′ = Et) was also hydrolysed with one equivalent of alkali to the half-ester (XI; R = H, R′ = Et); this was decarboxylated and the monoester subsequently hydrolysed to the same low-melting monobasic acid (II; R = R′ = R″ = H). Bromination of this gave a dibromo-acid (III; R = H) again isomeric with that previously obtained, but this, like its isomer, gave a product which could not be freed from bromine-containing impurities when dehydrobrominated. The two dibromo-acids differ somewhat in their ultra-violet spectra ($\lambda_{max.}$ at 238 and 249 mμ) but the configuration of the bromine atom has been reported to have an unexpectedly large influence on the absorption spectrum (Djerassi *et al.*, *loc. cit.*; Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066).

Experimental

Absorption spectra were determined with a Unicam quartz spectrophotometer, ethanol being the solvent unless otherwise stated.

Methyl 4-Methyl-3-oxocyclohexylacetate (I; R = Me).—This was prepared by a modification of the procedure described previously (Mukherjee, *loc. cit.*; Gunstone and Tulloch, *loc. cit.*): Ethyl 1-methyl-2-oxocyclohexane-1-carboxylate (368 g.) was stirred during addition of bromine (110 ml.) at 0° during 3 hr. With continued stirring, quinoline (350 ml.) was then added and

the mixture heated at 150—160° (bath) for 30 min., during which the temperature of the solution rose to 190°. Worked up as before, the ester (231 g., 64%), b. p. 124—128°/15 mm., absorption max. at 225 mμ (log ε 3·89), was obtained along with lower- and higher-boiling fractions both of which treated as subsequently described for the main fraction gave additional quantities of the acid (I; R = H).

Michael condensation of 1-methyl-2-oxo*cyclo*hex-3-ene-1-carboxylate with diethyl malonate in the presence of catalytic quantities of sodium ethoxide gave after 40 hr. a 74% yield.

Hydrolysis of this substituted malonic ester with concentrated hydrochloric acid (40 hr.) gave the *keto-acid* (I; R = H), b. p. 146—148°/0·4 mm., m. p. 67—88° raised to 88—97° by one crystallisation from carbon tetrachloride. Further crystallisation from this solvent hardly raised the m. p., and a second isomer could not be obtained. The acid crystallised from ether as colourless prisms, m. p. 95—99° (Found: C, 63·8; H, 8·3. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%); it gave a *semicarbazone*, m. p. 193—195° (decomp.), colourless prisms from methanol (Found: C, 53·0; H, 7·4; N, 18·7. $C_{10}H_{17}O_3N_3$ requires C, 52·9; H, 7·5; N, 18·5%), and a p-*bromophenacyl ester*, m. p. 93—95°, colourless leaflets from aqueous ethanol (Found: C, 55·9; H, 5·3; Br, 21·9. $C_{17}H_{19}O_4Br$ requires C, 55·6; H, 5·2; Br, 21·8%).

The acid, esterified by refluxing methanol and concentrated sulphuric acid for 16 hr., gave the *ester* (I; R = Me) (95%), b. p. 136—137°/13 mm., n_D^{18} 1·4627 (Found: C, 65·3; H, 8·6. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·8%).

1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthylacetic Acid* (II; R = Me, R′ = R″ = H).—A benzene solution of the keto-ester (I; R = Me) (50 g. in 250 ml.) was added to 1-diethylaminopentan-3-one methiodide (from 42·7 g. of the Mannich base and 38·6 g. of methyl iodide) at 0° and the mixture stirred at 0° under a stream of nitrogen during the dropwise addition of sodium (6·3 g.) dissolved in methanol (250 ml.) and subsequently for 2 hr. whilst the temperature rose to 20°. Next day the solution was heated with stirring on the steam-bath for 2 hr., then cooled and acidified (acetic acid, 16 ml.). After removal of most of the solvent under reduced pressure at room temperature, the solution was diluted with water and extracted with ether; acidic material was removed, re-esterified, combined with the main bulk, and distilled. A fore-run of starting material (31·7 g.) was followed by the ester (II; R = R′ = Me, R″ = H) (10·5 g.), b. p. 110—148°/0·3 mm., n_D^{20} 1·510—1·515, absorption max. at 250 mμ (log ε 3·94); the 2 : 4-*dinitrophenylhydrazone*, m. p. 176—177°, formed scarlet leaflets from acetic acid (Found: C, 58·7; H, 6·1; N, 13·1. $C_{21}H_{26}O_6N_4$ requires C, 58·6; H, 6·1; N, 13·0%).

Alkaline hydrolysis (5% sodium hydroxide solution, 3 hr.) gave a gum, approximately one half of which crystallised from ether. This *acid* (II; R = Me, R′ = R″ = H), recrystallised from ether–light petroleum (b. p. 40—60°), had m. p. 130—135°, absorption max. at 248 mμ (log ε 4·22) (Found: C, 71·3; H, 8·5. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%).

1 : 6-*Dibromo*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthylacetic Acid* (III; R = Me).—Bromine (1·02 g.) in acetic acid (10 ml.) was added dropwise with swirling during 1 hr. to a solution of the acid (II; R = Me, R′ = R″ = H) (0·75 g.) in ether (60 ml.) containing two drops of 4N-hydrogen bromide in acetic acid. The solvent was then removed at 25° under reduced pressure and the residue triturated with ether. The *dibromo-acid* (0·76 g.) solidified [m. p. 123—125° (decomp.)], and formed colourless prisms from benzene–light petroleum (b. p. 60—80°), soluble in 5% sodium carbonate solution, absorption max. at 253 mμ (log ε 4·04) (Found: C, 42·6; H, 4·7; Br, 40·6. $C_{14}H_{18}O_3Br_2$ requires C, 42·7; H, 4·6; Br, 40·6%).

Lactone (IV; R = Me, R′ = H) *of* 1 : 2 : 5 : 6 : 7 : 10-*Hexahydro*-1-*hydroxy*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthylacetic Acid*.—The dibromo-acid (III; R = Me, 700 mg.) was heated in collidine (20 ml.) to 170° during 30 min. and kept thereat for 90 min., then cooled. Benzene was added and the precipitate of collidine hydrobromide (88%) removed. The solution was then extracted with ice-cold 2N-hydrochloric acid and 5% sodium carbonate solution, and the neutral material (298 mg.) remaining after removal of the solvent was chromatographed on silica gel; the desired *lactone* (93 mg.) was eluted with chloroform. This crystallised from methanol–ether as colourless diamond-shaped prisms, m. p. 122—123°, absorption max. at 243 mμ (log ε 4·05), (cf. santonin, absorption max. at 242 mμ, log ε 4·14; Ruzicka, Cohen, Furter, and van der Sluys-Veer, *Helv. Chim. Acta*, 1938, **21**, 1735) (Found: C, 72·3; H, 6·7. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%).

Lactone (V; R = H) *of* 7-*Acetoxy*-1 : 2 : 3 : 4-*tetrahydro*-1-*hydroxy*-5 : 8-*dimethyl*-2-*naphthylacetic Acid*.—After being kept at room temperature for 4·5 hr. a mixture of the ketone (IV; R = Me, R′ = H) (44 mg.), acetic anhydride (2·2 ml.), and concentrated sulphuric acid (9 mg.)

was shaken with water (8 ml.), and the chloroform extract washed with water and with 5% sodium carbonate solution. The gum (38 mg.) remaining after removal of the solvent, when treated with ether, gave crystals (27 mg.) which, after recrystallisation from methanol–ether, afforded the desired *acetate* as colourless prisms, m. p. 148—149°, absorption max. at 273—280 mμ (log ε 3·23), min. at 246 mμ (log ε 2·70), and rising absorption below 210 mμ (log ε 4·32 at 206 mμ) [cf. values for (−)-α-desmotroposantonin acetate given below] (Found: C, 69·8; H, 6·7. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·6%).

(−)-α-*Desmotroposantonin Acetate* (V; R = Me).—Santonin (50 mg.) was converted into (−)-α-desmotroposantonin acetate, m. p. 154—156° (Huang-Minlon, Lo, and Chu, *J. Chinese Chem. Soc.*, 1943, **11**, 126 give 156—157°), absorption max. at 273—281 mμ (log ε 3·10), min. at 248 mμ (log ε 2·32), and rising absorption below 210 mμ (log ε 4·36 at 206 mμ).

1-*Bromo*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-8 : 10-*dimethyl*-7-*oxo*-2-*naphthylacetic Acid* (VII; R = Me, R′ = H).—A solution of the unsaturated keto-acid (II; R = Me, R′ = R″ = H) (150 mg.) in carbon tetrachloride (25 ml.) was refluxed with *N*-bromosuccinimide (120 mg.) and a trace of benzoyl peroxide for 2 hr. Succinimide was filtered from the cooled solution, the solvent removed at room temperature, and the residue treated with ether, yielding the *monobromo-acid* (115 mg.), m. p. 126—129° after crystallisation from ether–methanol–light petroleum (b. p. 40—60°) (colourless prisms), soluble in cold bicarbonate solution, absorption max. at 246 mμ (log ε 4·12) (Found: C, 53·0; H, 6·1. $C_{14}H_{19}O_3Br$ requires C, 53·3; H, 6·1%). After this had been refluxed with a solution from sodium (50 mg.) in ethanol (20 ml.) for 4 hr. a small amount of neutral product (m. p. 146—153°) was isolated, having an absorption max. at 246 mμ (log ε 4·02). This may have been the lactone (VIII; R = Me) but neither crystallisation nor chromatography gave an analytically pure specimen.

1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-10-*methyl*-7-*oxo*-2-*naphthylacetic Acid* (II; R = R′ = R″ = H).—This octalone ester was also prepared by using sodium methoxide as already described. Methyl iodide (39 g.), 1-diethylaminobutan-3-one (39 g.), keto-ester (I; R = Me) (50 g.), and sodium (6·3 g.) in the same solvents as before gave recovered keto-ester (28 g.) and the octalone ester (8·0 g.), b. p. 144—158°/0·4 mm., absorption max. at 239 mμ (log ε 4·11).

Less conveniently, the keto-ester (I; R = Me) (50 g.) was added dropwise during 30 min. to a stirred suspension of sodamide (from 15·6 g. of sodium) in dry ether (1 l.) at 10° under nitrogen. Stirring was continued for 1 hr. at 10° and for 5 hr. at room temperature and then a solution of 1-diethylaminobutan-3-one methiodide (Wilds and Shunk, *J. Amer. Chem. Soc.*, 1943, **65**, 469) [from 1-diethylaminobutan-3-one (39 g.) and methyl iodide (39 g.) in ethanol (45 ml.)] was added at 5° during 90 min. After a further hour's stirring the mixture was left over-night, then heated at 45° for 6 hr., decomposed with 2N-hydrochloric acid, and extracted with ether. The product which was entirely acidic was re-esterified and distilled. The octalone ester (II; R = R″ = H, R′ = Me) (7·7 g.), b. p. 152—180°/0·5 mm., n_D^{21} 1·5220, absorption max. at 239 mμ (log ε 4·05) [*semicarbazone*, m. p. 190—196° (Found: C, 61·4; H, 7·6; N, 14·2. $C_{15}H_{23}O_3N_3$ requires C, 61·4; H, 7·9; N, 14·3%)], was accompanied by a fore-run of starting material (I; R = Me) (25·2 g.).

Hydrogenated over 5% palladium–charcoal this ester gave methyl decahydro-10-methyl-7-oxo-2-naphthylacetate, n_D^{18} 1·4900 [*semicarbazone*, m. p. 188—191° (Found: C, 61·3; H, 8·2; N, 14·3. $C_{15}H_{25}O_3N_3$ requires C, 61·0; H, 8·5; N, 14·2%)]. Attempts to convert this into the ketone (IV; R = R′ = H) were unsuccessful (cf. Gunstone and Heggie, *J.*, 1952, 1437).

Alkaline hydrolysis of the octalone ester by the procedure described above gave the corresponding *acid* (II; R = R′ = R″ = H), m. p. 113—115°, absorption max. at 240 mμ (log ε 4·17) (Found: C, 70·4; H, 8·2. $C_{13}H_{18}O_3$ requires C, 70·2; H, 8·2%). Other low-melting samples were obtained but a pure second isomer could not be isolated.

1 : 6-*Dibromo*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-10-*methyl*-7-*oxo*-2-*naphthylacetic Acid* (III; R = H).—Bromination of the foregoing acid as described on p. 1133 gave the *dibromo-acid* (59% yield), m. p. 130—132° (decomp.), absorption max. at 238 mμ (log ε 4·06) (Found: C, 40·9; H, 4·5; Br, 42·5. $C_{13}H_{16}O_3Br_2$ requires C, 41·1; H, 4·2; Br, 42·1).

This dibromo-acid, with refluxing collidine, gave a *monobromo-lactone* (VI), m. p. 115—118° (decomp.), absorption max. at 240 mμ (log ε 4·06) (Found: C, 51·9; H, 5·1. $C_{13}H_{15}O_3Br$ requires C, 52·2; H, 5·1%). When heated with collidine to 170° during 1 hr. and at 170° for a further hour the neutral product (m. p. 168—172°) could not be obtained free from bromine-containing impurities.

Lactone (VIII; R = H) *of* 1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-1-*hydroxy*-10-*methyl*-7-*oxo*-2-*naphthylacetic Acid*.—The acid (II; R = R′ = R″ = H) (1·24 g.) was treated with *N*-bromosuccinimide (1·1 g.) and the crude monobromo-acid [m. p. 133—135° (decomp.)] was refluxed

with a solution of sodium (124 mg.) in ethanol (15 ml.) for 4 hr. The product, extracted with chloroform and washed with 5% sodium carbonate solution, crystallised from ether. This crude product (600 mg.) was crystallised from ether–methanol and chromatographed on silica gel; elution with benzene–chloroform (1 : 1) removed bromine-containing impurities, followed by the desired *lactone*, m. p. 136—137° after crystallisation from ether–methanol; it had an absorption max. at 235 mμ (log ε 4·14) (Found : C, 70·7; H, 7·4. $C_{13}H_{16}O_2$ requires C, 70·9; H, 7·3%).

Attempts to brominate this lactone with bromine or with *N*-bromosuccinimide gave only intractable gums. Reaction of the dibromo-acid with sodium ethoxide also gave uncrystallisable products.

2 : 3 : 4 : 5 : 6 : 7 : 8 : 10-*Octahydro*-10-*methyl*-2-*oxonaphthalene* (IX).—This was prepared (19·6 g.) by condensation of 1-diethylaminobutan-3-one methiodide (from 110 g. each of the ketone and of methyl iodide) with 2-methyl*cyclo*hexanone (86 g.) in the presence of sodium methoxide (from 16·5 g. of sodium) by the method already given.

2 : 3 : 4 : 5 : 6 : 10-*Hexahydro*-10-*methyl*-2-*oxonaphthalene* (X).—Bromination of the octalone (33 g.) with *N*-bromosuccinimide in the presence of benzoyl peroxide and subsequent dehydrobromination with collidine at 145° (cf. Gunstone and Tulloch, *loc. cit.*) gave the ketone (X) (15 g.), b. p. 80—86°/0·25 mm., n_D^{18} 1·5630, absorption max. at 281 mμ (log ε 4·22); this gave a 2 : 4-*dinitrophenylhydrazone*, m. p. 187—190°, lustrous deep crimson plates from acetic acid, absorption max. at 267, 307, and 401 mμ (log ε 4·20, 4·12, and 4·53) in $CHCl_3$ (Found : C, 59·7; H, 5·0; N, 16·4. $C_{17}H_{18}O_4N_4$ requires C, 59·6; H, 5·3; N, 16·4%).

Diethyl 1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-10-*methyl*-7-*oxo*-2-*naphthylmalonate* (XI; R = R′ = Et).—Diethyl malonate (19 g.) in ethanol (25 ml.) was added to sodium (2·42 g.) dissolved in anhydrous ethanol (35 ml.) under a stream of nitrogen, followed by the ketone (X) (17 g.) also in ethanol (25 ml.). The mixture was refluxed for 75 min., cooled, acidified (acetic acid, 6·5 ml.), and poured into brine (50% saturated; 300 ml.); the products were extracted with chloroform and washed with sodium hydrogen carbonate solution and with brine. Distillation gave the keto-ester (11·1 g.), b. p. 174—180°/0·2 mm., n_D^{20} 1·5105, absorption max. at 239 mμ (log ε 4·21), yielding a red 2 : 4-*dinitrophenylhydrazone*, m. p. 146—150° (from ethanol) (Found : C, 57·6; H, 5·8; N, 11·3. $C_{24}H_{30}O_8N_4$ requires C, 57·4; H, 6·0; N, 11·2%).

1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*Octahydro*-10-*methyl*-7-*oxo*-2-*naphthylmalonic Acid* (XI; R = R′ = H).—The ester (8 g.) hydrolysed with 3N-alcoholic potassium hydroxide (75 ml.) for 4 hr. after acidification, extraction with chloroform, and crystallisation from ether gave the *dibasic acid* (1·76 g.) which formed colourless prisms, m. p. 165—168° (decomp.) (from water), absorption max. at 239 mμ (log ε 4·24) (Found : C, 63·1; H, 6·7. $C_{14}H_{18}O_5$ requires C, 63·1; H, 6·8%). The aqueous solution which had been extracted with chloroform deposited more acid (1·54 g.) when concentrated.

1 : 2 : 3 : 4 : 5 : 6 : 7 : 8 : 10-*Octahydro*-10-*methyl*-7-*oxo*-2-*naphthylacetic Acid* (II; R = R′ = R″ = H).—The dibasic acid (2·44 g.) was decomposed at 205°/0·2 mm. during 10 min. The residue, treated with ether, gave an acid, m. p. 85—88° after crystallisation from ether–light petroleum (b. p. 60—80°), having an absorption max. at 240 mμ (log ε 4·19). The m. p. was unchanged when the acid was distilled *in vacuo*. Its p-*bromophenacyl ester* had m. p. 123—124° (Found : C, 59·7; H, 5·5. $C_{21}H_{23}O_4Br$ requires C, 60·1; H, 5·5%).

The same acid was obtained from the diester *via* the acid-ester thus : The diester (860 mg.) was refluxed with 0·5N-ethanolic potassium hydroxide (5·3 ml., 1 equiv.) for 2 hr. and worked up as described. Crystallised from ether at −20° and subsequently from benzene–light petroleum (b. p. 60—80°), the product gave *monoethyl* 1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-10-*methyl*-7-*oxo*-2-*naphthylmalonate* (XI; R = H, R′ = Et) (115 mg.), m. p. 142—145° (decomp.), absorption max. at 240 mμ (log ε 4·22) (Found : C, 65·0; H, 7·1. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%). When this was distilled at 160° (bath)/0·5 mm., decarboxylation occurred with formation of the ester (II; R = R″ = H, R′ = Et) [*semicarbazone*, m. p. 187—190°, needles from methanol (Found : C, 62·7; H, 8·0; N, 13·8. $C_{16}H_{25}O_3N_3$ requires C, 62·5; H, 8·2; N, 13·7%)]. The 2 : 4-*dinitrophenylhydrazone* of the methyl ester (II; R = R″ = H, R′ = Me) was obtained when prepared from the ethyl ester in methanol solution in presence of concentrated sulphuric acid, and had m. p. 76—78° (Found : C, 57·9; H, 5·7. $C_{26}H_{24}O_6N_4$ requires C, 57·7; H, 5·8%). The non-crystalline portion of the acid-ester was similarly decarboxylated and then hydrolysed to give the monobasic acid (II; R = R′ = R″ = H), m. p. 84—86°.

1 : 6-*Dibromo*-1 : 2 : 3 : 4 : 5 : 6 : 7 : 10-*octahydro*-10-*methyl*-7-*oxo*-2-*naphthylacetic Acid* (III; R = H).—The low-melting isomer of the acid (II; R = R′ = R″ = H) gave a *dibromo-acid*, m. p. 142—145° (decomp.), absorption max. at 249 mμ (log ε 4·03) (Found : C, 40·7; H, 4·4.

$C_{13}H_{16}O_5Br_2$ requires C, 41·1; H, 4·2%). Attempts to dehydrobrominate this acid with collidine again gave impure material containing bromine.

We are indebted to the D.S.I.R. for a Maintenance Allowance (to A. P. T.), to Miss C. E. A. Smith for assistance with early experiments in the alternative route to the acid (II; R = R′ = R″ = H), to Dr. G. Eglinton for the measurement and interpretation of the infra-red spectra, and to Mr. J. M. L. Cameron and Miss M. W. Christie for the microanalyses.

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Characterisation of Methyl 4 : 6-O-*Benzylidene-*α-D-*galactoside and of* 2 : 3-*Di*-O-*methyl-*D-*galactose.*

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Several derivatives of 2 : 3-di-*O*-methyl-D-galactose have been prepared; the aniline derivative, 2 : 3-di-*O*-methylgalactaro-1→4-lactone, and 2 : 3-di-*O*-methyl-D-galactonamide are suitable for its characterisation. The sugar and several of its derivatives had physical characteristics different from those previously reported. It is probable that only one form of methyl 4 : 6-*O*-benzylidene-α-D-galactoside has so far been obtained.

FIVE years ago we prepared 2 : 3-di-*O*-methyl-D-galactose, following the directions of Robertson and Lamb (*J.*, 1934, 1321), with the object of characterising more fully this non-crystallisable sugar. From the outset we were hindered by inability to prepare methyl 4 : 6-*O*-benzylidene-α-D-galactoside having the rotation reported by Robertson and Lamb (*loc. cit.*) ($[\alpha]_D$ +166·5° in $CHCl_3$) and later by Sorkin and Reichstein (*Helv. Chim. Acta*, 1945, **28**, 1) ($[\alpha]_D$ +162°). Although we used methyl α-D-galactoside with $[\alpha]_D$ close to the accepted value (Dale and Hudson, *J. Amer. Chem. Soc.*, 1930, **52**, 2534; Ault, Haworth, and Hirst, *J.*, 1935, 1012; Reeves, *J. Amer. Chem. Soc.*, 1949, **71**, 1737), and followed the procedure of Sorkin and Reichstein (*loc. cit.*), our product had $[\alpha]_D$ +144°. We were convinced that we were handling the pure substance, since we could regenerate it from its crystalline diacetate without change in $[\alpha]_D$. Further, a specimen prepared in this Laboratory by the late Mr. S. Williamson by the distillation method used by Robertson and Lamb (essentially that of Irvine and Scott, *J.*, 1913, 575) was found by us to have, after recrystallisation, the same melting point and rotation. About this time Reeves (*loc. cit.*) reported $[\alpha]_D$ +142°; and Dr. J. G. Buchanan of the Lister Institute (personal communication) informs us that he has been unable to prepare this substance with properties other than those found by Reeves and ourselves.

Fletcher, Diehl, and Ness recently (*J. Amer. Chem. Soc.*, 1954, **76**, 3029) also found +144°, and inferred the existence of two forms of this compound, differing through enantiomorphism of the benzylidene grouping. We therefore communicated with Professor Reichstein about this matter, with the result that Dr. Tamm, at Basle, re-examined Sorkin and Reichstein's original specimen finding m. p. 168—170° (Kofler block) and $[\alpha]_D^{21}$ +142·1° ± 1° in $CHCl_3$. Although our material underwent slight decomposition on storage, unless sealed with a trace of ammonia, a specimen from Basle shows no sign of breakdown. Professor Reichstein has kindly authorised us (August 28th, 1954) to make known these corrected values, and states: "The published figure must therefore be due to an error. It is impossible to trace the reason now." Robertson and Lamb's values must likewise be due to some error which cannot now be explained. The specimen labelled "4 : 6-benzylidene-α-methyl galactoside" obtained from the St. Andrews laboratory through the kind co-operation of Professor J. Read, F.R.S., and Dr. E. S. Steele was found by us to be an impure specimen of the β-glycoside. We believe that only one form of methyl 4 : 6-*O*-benzylidene-α-D-galactoside has so far been prepared, but whether or not this is homogeneous with respect to a single "benzylidene enantiomorph" remains undecided.

In the preparation of 2 : 3-di-*O*-methylgalactose and its derivatives (see scheme annexed) we obtained other products with physical characteristics different from those given in the literature (see Table). In particular, (i) the sugar, which is very difficult to free from solvents, had a much higher $[\alpha]_D$ (*c* determined by hypoiodite reduction) than previously reported; (ii) methyl 2 : 3-di-*O*-methyl-α-galactoside had $[\alpha]_D$ lower than that given by Robertson and Lamb (*loc. cit.*), and not raised by regeneration of the compound from its 4 : 6-dinitrate (which itself had different characteristics from those reported by Robertson and Lamb); the refractive index was also different; and (iii) the aniline derivative of the sugar was quite unlike the substance described by Robertson and Lamb, which was said to have been crystallised from "alcohol"; our product was extremely soluble in ethanol.

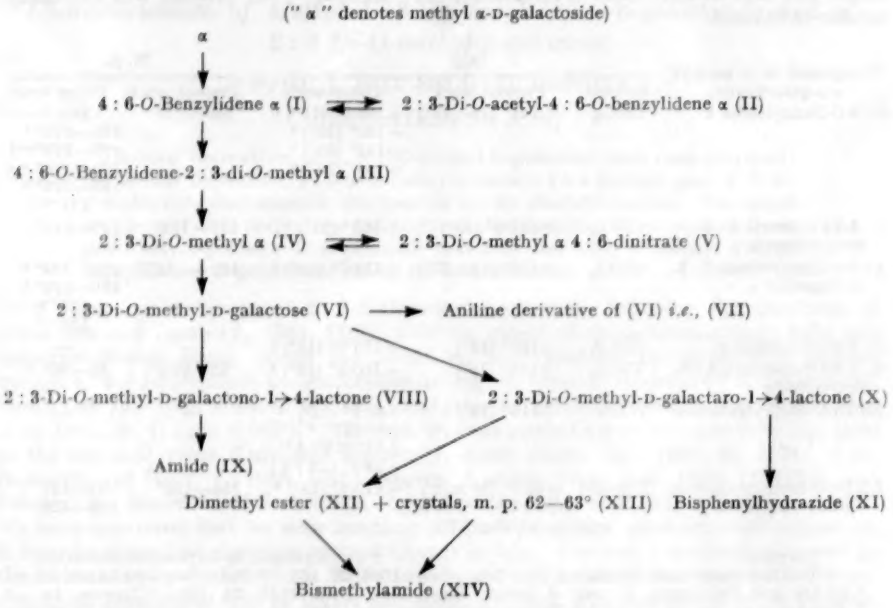
Compound (α = methyl α-D-galactoside)	$[\alpha]_D$			M. p.	
	Solvent	Present work	Other work	Present work	Other work
4 : 6-*O*-Benzylidene α	$CHCl_3$	+144° (17—21°)	+166·5° (15°) [2] +162° (15°) [3] +142° (25°) [5] +144° (20°) [6]	169—170°	152° [1] 170—172° [3] 177—178° * [5] 170—172° * [4] 168—169° [5] 171° [6]
2 : 3-Di-*O*-acetyl-4 : 6-*O*-benzylidene α	$CHCl_3$	+211·5° (19°)	+198° (21°) [7]	117—118°	117—118° [7]
4 : 6-*O*-Benzylidene-2 : 3-di-*O*-methyl α	$CHCl_3$	+170° (18—22°)	+173·7° (15°) [3]	126·5—127°	123—124° [2] 128—129° [3] 125° [9] 120° [11]
2 : 3-Di-*O*-methyl α	$CHCl_3$	+167° (19°)	+173·7° (15°) [2]	—	—
2 : 3-Di-*O*-methyl α 4 : 6-di-*O*-nitrate	$CHCl_3$	+114° (19°)	+100·3° (15°) [2]	95—95·5°	88—90° [2]
2:3-Di-*O*-methylgalactose	Water	+116° (19°) †	+80·9° (22°) [10] −2° (17°) [9] +71° (23°) † [11] +78·5° (23°) † [11]	—	—
2:3-Di-*O*-methylgalactose aniline derivative	Ethanol	−56·8° (20 min.) → +12·1° (121 hr., equil.; 17°)	+119·4° (15°) [2]	154—155°	130—131° [2] 128—129° [10]

* Corrected. † *c* determined by hypoiodite reduction.

[1] Van Eckenstein and Blanksma, *Rec. Trav. chim.*, 1906, **25**, 153. [2] Robertson and Lamb, *loc. cit.* [3] Sorkin and Reichstein, *loc. cit.* [4] Tamm, *Helv. Chim. Acta*, 1949, **32**, 163. [5] Reeves, *loc. cit.* [6] Fletcher *et al.*, *loc. cit.* [7] Müller, Móricz, and Verner, *Ber.*, 1939, **72**, 745. [8] Reber and Reichstein, *Helv. Chim. Acta*, 1945, **28**, 1164. [9] Luckett and Smith, *J.*, 1940, 1106. [10] Pascu and Trister, *J. Amer. Chem. Soc.*, 1940, **62**, 2301. [11] Bolliger and Schmid, *Helv. Chim. Acta*, 1954, **37**, 888.

The aniline derivative is suitable for characterisation of the sugar. Crystalline 2 : 3-di-*O*-methylgalactono-1→4-lactone, obtained by oxidation of the sugar with bromine water, is extremely deliquescent but yields a satisfactory amide. We have also investigated 2 : 3-di-*O*-methylgalactaric acid derivatives. Beavan and Jones (*J.*, 1947, 1218) oxidised 2 : 3-di-*O*-methyl-D-galacturonic acid with bromine water and obtained a syrup, stated to be 2 : 3-di-*O*-methyl-D-galactaric acid (methoxyl content and equivalent determined). Luckett and Smith (*loc. cit.*) by a similar reaction prepared the acid barium salt (no analysis given); they also oxidised 2 : 3-di-*O*-methylgalactose (made according to Robertson and Lamb) with nitric acid to an acid product. Reeves (*J. Amer. Chem. Soc.*, 1948, **70**, 3963) hydrolysed and oxidised methyl 4 : 6-*O*-benzylidene-2 : 3-di-*O*-methyl-β-D-galactoside with nitric acid, but again the product was not analysed. All these workers esterified the oxidation product, obtaining, after high-vacuum distillation, 2 : 3-di-*O*-methyl-D-galactaric 1→4-lactone methyl ester. For this Luckett and Smith give m. p. 92°, Beavan and Jones 77—78°, raised to 96° by drying *in vacuo*, and Reeves 72—74°. Reeves gives no analysis, but suggests that his compound represents a different crystal modification from that of Luckett and Smith, since its melt, inoculated with their material, crystallised and then melted at 92°. Luckett and Smith converted the lactone-ester into the bismethylamide, and Reeves obtained the same compound.

On oxidising 2 : 3-di-*O*-methylgalactose with nitric acid (more dilute than that used by Luckett and Smith) we obtained crystalline 2 : 3-di-*O*-methyl-D-galactaro-1→4-lactone. On esterification a crystalline product was obtained without distillation. A single recrystallisation, however, separated this into two fractions: (XII) the dimethyl ester of 2 : 3-di-*O*-methyl-D-galactaric acid, m. p. 95—96°, and (XIII) crystals, m. p. 62—63°. Elementary and methoxyl analyses suggested that (XIII) consisted of a mixture of the dimethyl ester and the ester-lactone. It is, however, noteworthy that these crystals were obtained in two separate preparations, and that their melting point was unaffected by further recrystallisation. Both (XII) and (XIII) gave the bismethylamide in good yield.


(" α " denotes methyl α-D-galactoside)
α
4 : 6-O-Benzylidene α (I)
2 : 3-Di-O-acetyl-4 : 6-O-benzylidene α (II)
4 : 6-O-Benzylidene-2 : 3-di-O-methyl α (III)
2 : 3-Di-O-methyl α (IV)
2 : 3-Di-O-methyl α 4 : 6-dinitrate (V)
2 : 3-Di-O-methyl-D-galactose (VI)
Aniline derivative of (VI) i.e., (VII)
2 : 3-Di-O-methyl-D-galactono-1→4-lactone (VIII)
2 : 3-Di-O-methyl-D-galactaro-1→4-lactone (X)
Amide (IX)
Dimethyl ester (XII) + crystals, m. p. 62—63° (XIII)
Bisphenylhydrazide (XI)
Bismethylamide (XIV)

Experimental

M. p.s and rotations (measured in 2-dm. tubes unless otherwise stated) were determined on specimens dried over phosphoric oxide at *ca.* 0·01 mm. and room temperature. Evaporations were done under reduced pressure below 50°, and solvents distilled in glass used for recrystallisations. Equivalent weights of lactones were determined by treatment with aqueous sodium hydroxide in 25% excess for 4—6 hr. at room temperature and back-titration with hydrochloric acid, with exclusion of carbon dioxide throughout. pH was measured by the glass electrode. We thank Dr. D. H. Northcote for some of the methoxyl determinations.

Methyl 4 : 6-O-*Benzylidene-*α-D-*galactoside* (I).—In accord with the work by Dale and Hudson (*loc. cit.*) and Ault, Haworth, and Hirst (*loc. cit.*), crude methyl α-D-galactoside was purified through the tetra-*O*-acetyl derivative, $[\alpha]_D^{19}$ +133° (*c*, 6·1 in $CHCl_3$) (Dale and Hudson, *loc. cit.*, give +133°). After recrystallisation from ethanol and drying over phosphoric oxide at 90—95°/0·01 mm. the purified galactoside had $[\alpha]_D^{17}$ +195·1° (*c*, 1·8 in H_2O) and m. p. 123—125°. (The anhydrous galactoside readily forms the monohydrate in air, and pressing the material on porous plate lowered the m. p. considerably. Ault *et al.*, *loc. cit.*, give m. p. 116°.) It was converted into the benzylidene compound (I) by Freudenberg's method (*Ber.*, 1928, **61**, 1728), following Sorkin and Reichstein (*loc. cit.*); recrystallised from ethanol or ethanol–light petroleum (b. p. 60—80°) this had $[\alpha]_D^{20}$ +168° (*c*, 2·3 in MeOH); for m. p. and $[\alpha]_D$ in $CHCl_3$ (*c*, 1·8—2·1) see Table (Found: C, 59·7; H, 6·4. Calc. for $C_{14}H_{18}O_6$: C, 59·6; H, 6·4%).

Our material was somewhat unstable; after 3 months in a desiccator it smelt of benzaldehyde and had m. p. 165—167°. However, after 4 years in a sealed tube a sample smelt only faintly

of benzaldehyde and had m. p. **168—169°**, or sealed with a trace of ammonia had unchanged m. p. and no smell after the same period. To test the possibility that the high m. p.s and rotations given by some authors resulted from overheating of the preparation, a sample was heated for 2 hr. at 96—100°/0·3 mm.; it lost only 0·2% in weight, and the m. p. and $[\alpha]_D$ were not raised.

The 2 : 3-di-*O*-acetate (II), prepared from (I) by the procedure of Müller, Móricz, and Verner (*loc. cit.*), had, after three recrystallisations from aqueous ethanol, the m. p. and $[\alpha]_D$ (*c*, 1·5) given in the Table (not raised by further recrystallisation) (Found : C, 59·2; H, 6·15; Ac, 23·5. Calc. for $C_{18}H_{32}O_8$: C, 59·0; H, 6·0; Ac, 23·5%). The acetate (II) was reconverted into (I) by 30 minutes' boiling with ethanolic sodium hydroxide. The product (95% yield) had m. p. 168—169° and $[\alpha]_D^{18}$ +141° in $CHCl_3$, and after one recrystallisation from ethanol 169—170° and +143·5° respectively.

Methyl 2 : 3-*Di*-O-*methyl*-α-D-*galactoside* (IV).—The galactoside (I), dissolved in acetone, was treated with methyl sulphate and aqueous sodium hydroxide, giving methyl 4 : 6-*O*-benzylidene-2 : 3-di-*O*-methyl-α-D-galactoside (III) (77%), m. p. 124—125°, $[\alpha]_D^{22}$ +170° (*c*, 2·0 in $CHCl_3$) after one recrystallisation from ether. Further recrystallisations from acetone–light petroleum (b. p. 60—80°) and ether–acetone raised the m. p. to 126·5—127°, with no change in $[\alpha]_D$ (Found : C, 61·9; H, 6·85; OMe, 30·2. Calc. for $C_{16}H_{22}O_6$: C, 61·9; H, 7·1; OMe, 30·0%). The derivative (III) was converted into the methylgalactoside (IV) by Robertson and Lamb's method (*loc. cit.*) except that the product was extracted by anhydrous ether–absolute ethanol instead of acetone. It was distilled at 0·05 mm. and collected in three fractions (bath-temp. 150—173°) which had the following n_D^{28} and $[\alpha]_D^{19}$ in $CHCl_3$: (i) (10%) 1·4771, +165°; (ii) (53%) 1·4773, +167°; (iii) (28%) 1·4773, +167° [Found for fraction (iii) : C, 49·0; H, 8·1. Calc. for $C_9H_{16}O_6$: C, 48·65; H, 8·1%]. Another preparation also had n_D^{28} 1·4773 (decrement for rise of 1°, 0·00029 from 17° to 30°). Our value for n_D^{15}, 1·4811, obtained by extrapolation from n_D^{17}, differs considerably from 1·4720 found by Robertson and Lamb (*loc. cit.*). $[\alpha]_D^{19}$ was +209° (*c*, 2·2 in H_2O).

The 4 : 6-di-*O*-nitrate (V), prepared from the galactoside (IV) by fuming nitric acid in chloroform had, after two recrystallisations from ethanol, the m. p. and $[\alpha]_D$ (*c*, 1·6) given in the Table (Found : C, 34·8; H, 5·3; N, 8·75. Calc. for $C_9H_{16}O_{10}N_2$: C, 34·6; H, 5·1; N, 8·95%). It was reconverted into (IV) with zinc and iron in glacial acetic acid; after distillation at 0·01 mm. with rejection of the first runnings, the regenerated galactoside was obtained in 62% yield, with n_D^{28} 1·4771, $[\alpha]_D^{19}$ +164° in $CHCl_3$ and +205° in H_2O.

Methyl 2 : 3-*Di*-O-*methyl*-β-D-*galactoside*.—The β-*galactoside* had been prepared in this Laboratory by the late Mr. S. Williamson from the 4 : 6-*O*-benzylidene derivative (Oldham and Bell, *J. Amer. Chem. Soc.*, 1938, **60**, 323). After distillation at 0·05 mm. it was a syrup, $[\alpha]_D^{18}$ +23·0° (*c*, 7·4 in H_2O), −10·7° (*c*, 6·8 in $CHCl_3$), n_D^{20} 1·4787 (decrement for rise of 1°, 0·00033 from 17° to 30°) (Found : C, 49·1; H, 8·1. $C_9H_{16}O_6$ requires C, 48·65; H, 8·1%).

2 : 3-*Di*-O-*methyl*-D-*galactose* (VI).—The galactoside (IV) was hydrolysed as directed by Robertson and Lamb (*loc. cit.*). The product was dissolved in dichloroethane, the solution filtered and evaporated, and the residue dried over phosphoric oxide at 43°/0·2 mm. for 3 hr. It gave a single compact spot on a paper chromatogram (butanol–water) and had $[\alpha]_D^{17}$ (*c*, 1·8 in H_2O) +76° (10 min.), +97° (6·5 hr., equil.). Further drying over phosphoric oxide at 70—75°/0·2 mm. for 3 hr. caused a 6·2% loss in weight; the sugar was now a colourless, hygroscopic, very viscous syrup, $[\alpha]_D^{18}$ (*c*, 1·5 in H_2O) +57° (5 min.), +74° (10 min.), +105° (140 min., equil.). The mutarotation is unusually large for a syrupy sugar. Another preparation (3·0 g.), which had been kept at 40—50°/0·2 mm. for 4 hr., was dissolved in water, the solution was evaporated to remove traces of organic solvents, and the residue was dissolved in water and filtered (charcoal). This process was repeated, the sugar being finally in 100 ml., and the rotation measured. Reduction of hypoiodite was determined under Macleod and Robison's conditions (*Biochem. J.*, 1929, **23**, 517) but on a larger scale (12 mg. of sugar); it was complete in 30 min. With *c* (2·43), thus determined, $[\alpha]_D^{19}$ was 116° in H_2O (*l*, 4). To test if this high $[\alpha]_D$ was due to presence of galactoside or anhydro-compounds the sugar was heated with N-hydrochloric acid at 95—100° for 2 hr. After working up and removal of traces of organic solvents, as before, $[\alpha]_D^{19}$ was +113° (*c*, 3·19 in H_2O, determined by hypoiodite; *l*, 4).

Aniline Derivative (VII).—After removal of impurities with ether–light petroleum (b. p. 40—60°), the derivative (VII) was crystallised from *n*-butanol–light petroleum (b. p. 40—60°), then twice from acetone; for m. p. and $[\alpha]_D$ (*c*, 3·6) see Table (Found : C, 59·2; H, 7·4; N, 4·95; OMe, 22·3. Calc. for $C_{14}H_{21}O_5N$: C, 59·4; H, 7·4; N, 4·95; OMe, 21·9%). At the end of the polarimetric observations the solution was allowed to evaporate; one

recrystallisation of the crystalline residue from acetone gave an almost quantitative recovery of material, m. p. 153—154°. The changing rotation was therefore not due to decomposition.

2 : 3-*Di*-O-*methyl*-D-*galactono*-1→4-*lactone* (VIII).—The sugar (VI), in 6% solution in water, was treated with bromine for 43 hr. The product was distilled at 0·1 mm. (bath-temp. 180—190°). The crystalline distillate was spread on porous plate at −10°, and the plate transferred to a desiccator containing phosphoric oxide. The crystals were washed by decantation with anhydrous ether at room temperature and dissolved in boiling anhydrous ether, and the solution decanted or filtered, and allowed to crystallise at −10°. The *lactone*, highly deliquescent colourless needles, neutralised 1·03 equiv. of sodium hydroxide. $[\alpha]_D^{19}$ (*c*, 1·9 in H_2O; *l*, 1) −48·8° (18 min.), −46·2° (26 hr.), −41·2 (100 hr.), −36·2° (270 hr., equil.). The rate of hydrolysis indicates a γ-lactone. A 1% solution in water had the following pH values (21°): 4·17 (initially); 2·90 (2 days); 2·79 (25 days).

2 : 3-*Di*-O-*methyl*-D-*galactonamide* (IX).—The lactone (VIII), with ammonia in methanol for 4 days at room temperature, gave the *amide* in 53% yield after recrystallisation from ethanol–acetone; this had m. p. 140° (not raised by further recrystallisation from ethanol), $[\alpha]_D^{20}$ +13·1° (*c*, 2·0 in H_2O) (Found: C, 42·9; H, 7·35; N, 6·5; OMe, 27·6. $C_9H_{17}O_6N$ requires C, 43·0; H, 7·6; N, 6·3; OMe, 27·8%). The phenylhydrazide was unstable and could not be recrystallised.

2 : 3-*Di*-O-*methyl*-D-*galactaro*-1→4-*lactone* (X).—The sugar (VI) was oxidised with nitric acid (*d*, 1·15) on the boiling-water bath. After removal of the nitric acid, the product was crystallised twice from ether, giving the *lactone* (X) (50%) as colourless crystals, stable in air, m. p. 126—126·5° (not raised by further recrystallisation) (Found: C, 43·8; H, 5·3; OMe, 28·1%; equiv., 110. $C_8H_{12}O_7$ requires C, 43·6; H, 5·45; OMe, 28·2%; equiv., 110), $[\alpha]_D^{18}$ (*c*, 2·0 in H_2O) −55·4° (8 min.), −51·3° (8·75 hr.), −38·6° (49 hr.), −28·7° (101 hr.), −18·3° (198 hr.), −13·4° (275 hr.), −11·0° (370 hr., equil.). The rate of hydrolysis indicates a γ-lactone. A 1% solution in water had the following pH values (21°): 2·22 (initially); 2·22 (2 days); 2·30 (6 days); 2·31 (25 days).

2 : 3-*Di*-O-*methyl*-D-*galactaric Bisphenylhydrazide* (XI).—The bisphenylhydrazide, obtained by heating the lactone (X) under reflux with phenylhydrazine and enough ethanol to effect dissolution, was obtained, after removal of impurities with ether, as colourless crystals, m. p. 140° (decomp.), from ethanol–ether. The m. p. was not raised by further recrystallisation from ethanol–ether or ethyl acetate–ether, but a satisfactory elementary analysis could not be obtained, probably because of some decomposition during recrystallisation (Found: C, 55·7; H, 6·5; N, 12·8; OMe, 15·3. Calc. for $C_{20}H_{24}O_6N_4$: C, 57·4; H, 6·2; N, 13·4; OMe, 14·8%). The substance decomposes in ethanol solution at room temperature, but $[\alpha]_D^{20}$ in ethanol remains at approx. +17° for several hours.

Dimethyl 2 : 3-*Di*-O-*methyl*-D-*galactarate* (XII).—The lactone (X) (0·83 g.) was heated under reflux for 10 hr. with 2% (w/v) hydrogen chloride in methanol. The crystalline product was recrystallised from ether–light petroleum (b. p. 40—60°) with a little chloroform. The first crop (0·38 g.) consisted of the *dimethyl ester* (XII), m. p. 95—96° (not raised by further recrystallisation), $[\alpha]_D^{18}$ (*c*, 1·0 in H_2O) +12·7° (7 min.), +7·3° (20 hr.), +3·4° (69 hr.), +0·8° (123 hr.), −3·6° (292 hr., constant); pH of 1% solution in water (16—18°), 4·45 (initially), 3·00 (5 days), 2·75 (16 days) (Found: C, 45·2; H, 6·9; OMe, 46·8. $C_{10}H_{18}O_8$ requires C, 45·1; H, 6·8; OMe, 46·6%). The second (0·34 g.) and the third (0·12 g.) crop had m. p. 62—63° and 61—62° respectively; this material (XIII), on further recrystallisation from ether, yielded three crops, 0·38 g. in all, each of m. p. 62—63° (Found: C, 45·8; H, 6·4; OMe, 42·7. Calc. for the lactone-ester $C_9H_{14}O_7$: C, 46·1; H, 6·0; OMe, 39·7%. For $C_{10}H_{18}O_8$ see above); these had $[\alpha]_D^{18}$ (*c*, 1·1 in H_2O) −22·2° (7 min.), −20·6° (18 hr.), −15·7° (77 hr.), −13·3° (122 hr.), −5·4° (30 days), −4·0° (34 days). The solution, originally neutral, became acid to Congo-red. The polarimetric behaviour is consistent with the crystals' being a mixture of dimethyl ester and lactone-ester; for the latter Luckett and Smith (*loc. cit.*) found $[\alpha]_D^{19}$ −56° (initial), −4° (29 days, constant).

The ester (XII) (122 mg.) and the material (XIII) (125 mg.) were separately treated with 25 ml. of 1·5N-methylamine in methanol for 2 days at room temperature. The methylamine was generated from hydrochloride which had been recrystallised from *n*-butanol to remove ammonium chloride. After recrystallisation from ethanol–ether both specimens of bismethylamide (XIV) [105 mg. from (XII) and 99 mg. from (XIII)] had m. p. 181—182° (uncorr.) [183·5—184·5° (corr.)] (not raised by further recrystallisation), $[\alpha]_D^{18}$ −7·7° (*c*, 2·5 in H_2O). Luckett and Smith (*loc. cit.*) give m. p. 184°, $[\alpha]_D^{18}$ −7·5°.

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Collision Parameters of C_6—C_9 Hydrocarbons in the Vapour Phase: The Hydrogen Effect.

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With nitrogen and hydrogen as carrier gases mass-diffusion coefficients have been measured for the compounds hexa-1 : 5-diene, 2 : 3-dimethylbuta-1 : 3-diene, 2 : 3-dimethylbut-2-ene, *n*-heptane, and *n*-nonane. These supply missing information in the gas-kinetic parameters for the C_6—C_9 range.

Results extend previous evidence that on the average the flexible hydrocarbons are substantially crumpled at normal temperatures in the vapour phase. Differences in effective hydrocarbon-collision diameters for hydrogen–hydrocarbon and nitrogen–hydrocarbon collisions (the "hydrogen effect") are discussed with reference to the influence of molecular flexibility, inelastic collisions, and the nature of the intermolecular potential. A marked hydrogen effect is found for the more flexible hydrocarbons.

Numerical trends as a function of molecular structure in collision parameters deduced from viscosity data (Cummings, McCoubrey, and Ubbelohde, *J.*, 1952, 2725) indicated substantial crumpling of flexible hydrocarbons in the vapour phase at normal temperatures. Collision parameters deduced for mass-diffusion (Cummings and Ubbelohde, *J.*, 1953, 3751) in nitrogen–hydrocarbon systems confirmed this and showed the general trends apparent in momentum-transfer parameters. Hydrocarbon "diameters" in collisions with hydrogen have been found to be greater than for the corresponding collisions with nitrogen when the hydrocarbon molecule is flexible. This effect was tentatively attributed to the occurrence of inelastic collisions. The present research has been undertaken in order to extend the previous findings to fresh examples in the C_6—C_9 range of hydrocarbons.

Experimental

Materials.—The preparation and purification of hexa-1 : 5-diene, 2 : 3-dimethylbuta-1 : 3-diene, and 2 : 3-dimethylbut-2-ene have been described by Cummings, McCoubrey, and Ubbelohde (*loc. cit.*). The properties of the purified samples will be given elsewhere (Cummings and McLaughlin, in the press). Samples of 99·9 mole-% *n*-heptane (b. p. 98·4°/760 mm., n_D^{20} 1·3876) and *n*-nonane (b. p. 150·8°/760 mm., n_D^{20} 1·4055) were gifts from the Anglo-Iranian Oil Co., to whom thanks are offered for their support of this work.

Apparatus and Technique.—The apparatus and technique for measuring mass diffusion were as described previously (Cummings and Ubbelohde, *loc. cit.*). Special precautions were taken in the handling of the unsaturated compounds (Howard, Mears, Fookson, Pomerantz, and Brooks, *J. Res. Nat. Bur. Stand.*, 1947, **38**, 365). The diffusion coefficient, D_{12} (cm.²/sec.), corrected to standard pressure was calculated from the equation:

$$D_{12}^{760} = \frac{(h_2^2 - h_1^2)d_e P}{2(t_2 - t_1)d_s \times 760 \ln [P/(P - P_s)]} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

which assumes perfect gas laws. h_1 is the height of the gas–vapour diffusion column at time t_1, and h_2 that at time t_2. d_e is the density of the liquid (g./ml.) d_s that of the saturated vapour, and P_s the saturation vapour pressure (cm.) at the temperature of experiment. The average total pressure (cm.) for the duration of the experiment is denoted by P.

Vapour-pressure data are available for *n*-heptane (Nat. Bur. Stand., Circular C461, 1947) and *n*-nonane (Rossini, Forziati, and Norris, *J. Res. Nat. Bur. Stand.*, 1949, **43**, 555). Measurement of the vapour pressures of the unsaturated hydrocarbons are reported elsewhere (Cummings and McLaughlin, in the press).

During the approximate three-hour periods between successive observations the average pressure and temperature fluctuations did not exceed $\pm 0{\cdot}2$ mm. and $\pm 0{\cdot}05°$ respectively. Diffusion coefficients calculated from equation 1 are recorded in Table 1, together with standard deviations.

TABLE 1.

Compound	Carrier gas	Temp. (°K)	D_{12}^{290} (cm.²/sec.)	No. of observations	Precision of D_{12} (±)
Hexa-1 : 5-diene	H_2	288·1	0·298	15	0·005
	N_2	288·1	0·0772	12	0·0015
2 : 3-Dimethylbuta-1 : 3-diene	H_2	288·1	0·312	9	0·005
	N_2	288·1	0·0748	6	0·0025
2 : 3-Dimethylbut-2-ene	H_2	288·1	0·296	8	0·006
	N_2	288·3	0·0705	8	0·0013
n-Heptane	H_2	303·0	0·286	12	0·004
	N_2	303·0	0·0743	8	0·0012
n-Nonane	H_2	339·8	0·284	7	0·002
	N_2	339·8	0·0737	8	0·0003

DISCUSSION

The heteromolecular collision cross-section σ_{12} can be defined in various ways depending on the form of the assumed intermolecular potential. Earlier results have been interpreted wholly on the basis of the rigid-sphere model. In this analysis (Chapman and Cowling, "Mathematical Theory of Non-Uniform Gases," Cambridge Univ. Press, 1939) the molecules are treated as hard rigid elastic spheres and the cross-section σ_{12} is defined by

$$(D_{12})_1 = \frac{3}{8n\sigma_{12}^2}\left\{\frac{kT(m_1+m_2)}{2\pi m_1 m_2}\right\}^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $(D_{12})_1$ is the first approximation for the diffusion coefficient, and the other symbols have their usual significance. For the more realistic Lennard-Jones potential of the form

$$V(r) = 4\varepsilon_{12}[(\sigma_{12}/r)^{12} - (\sigma_{12}/r)^6]$$

which takes account of the fact that molecules have superimposed attractive and repulsive force fields, the cross-section σ_{12} is defined by

$$(D_{12})_1 = \frac{3}{16n\sigma_{12}^2}\left\{\frac{kT(m_1+m_2)}{2\pi m_1 m_2}\right\}^{\frac{1}{2}} \frac{1}{W^1(1\,;\ kT/\varepsilon_{12})} \quad . \quad . \quad . \quad . \quad (3)$$

where $W^1(1\,;\ kT/\varepsilon_{12})$, the collision integral, is a tabulated function (Hirschfelder, Bird, and Spotz, *J. Chem. Phys.*, 1948, **16**, 968) of kT/ε_{12}, the force constant for the heteromolecular interaction. Table 2 gives the values of the cross-sections evaluated on the

TABLE 2. *Calculated cross-sections for hydrocarbons* (σ_{22}) (*mass transport*) (Å).

Compound	Rigid-sphere model			12 : 6 Model		
	N_2	H_2	Δ	N_2	H_2	Δ
n-Hexane *	6·51	6·78	+0·27	5·72	6·82	+1·10
Hexa-1 : 5-diene	6·41	6·60	+0·19	5·38	6·18	+0·80
2 : 3-Dimethylbutane *	6·53	6·60	+0·07	6·13	6·65	+0·52
2 : 3-Dimethylbuta-1 : 3-diene	6·57	6·39	−0·18	6·23	6·50	+0·27
2 : 3-Dimethylbut-2-ene	6·87	6·63	−0·24	6·89	6·99	+0·10
*cyclo*Hexane *	6·58	6·30	−0·28	6·08	6·34	+0·26
n-Heptane †	6·88	7·15	+0·27	5·96	6·96	+1·0
n-Octane *	6·94	7·31	+0·37	6·34	7·27	+0·93
2 : 2 : 4-Trimethylpentane * †	7·02	7·05	+0·03	6·61	7·12	+0·51
n-Nonane	7·74	8·07	+0·33	7·64	8·44	+0·80

* Values included in Table 2 from earlier work for convenience.

† ε/k for *n*-heptane and *iso*octane are derived from the empirical relation $\varepsilon/k = 1{\cdot}39T_b$ (Hirschfelder, Bird, and Spotz, *Trans. Amer. Soc. Mech. Eng.*, 1949, **71**, 921).

basis of equations 2 and 3. The requisite values of kT/ε were taken from viscosity data for the pure components (Cummings, McCoubrey, and Ubbelohde, *loc. cit.*; Hirschfelder, Curtiss, and Bird, "The Molecular Theory of Gases and Liquids," Wiley & Sons, Inc., New York, 1954) and kT/ε_{12} and σ_{22} were evaluated by using the empirical relations:

$$\varepsilon_{12} = (\varepsilon_{11}\varepsilon_{22})^{\frac{1}{2}}$$

$$\sigma_{12} = \tfrac{1}{2}(\sigma_{11} + \sigma_{22})$$

where σ_{11} and σ_{22} are the cross-sections for the carrier gas and hydrocarbon respectively. Table 2 also contains cross-sections calculated from the results of Cummings and Ubbelohde (*loc. cit.*) on the basis of the Lennard-Jones 12 : 6 potential. Values quoted in the above paper have been corrected for a small pressure term as explained in a forthcoming note.

The quantity Δ in Table 2 is defined by :

$$\Delta = \sigma_{22}(H_2) - \sigma_{22}(N_2)$$

where $\sigma_{22}(H_2)$ is the cross-section for the hydrocarbon when in collision with hydrogen and $\sigma_{22}(N_2)$ that when in collision with nitrogen. The values of $\sigma_{11}(H_2)$ and $\sigma_{11}(N_2)$ are obtained from Johnston and McCloskey's viscosity results (*J. Phys. Chem.*, 1940, **44**, 1038). On the rigid-sphere model $\sigma_{11}(N_2)$ is 3·75 and $\sigma_{11}(H_2)$ is 2·73 Å, while on the Lennard-Jones 12 : 6 model $\sigma_{11}(N_2)$ is 3·68 and $\sigma_{11}(H_2)$ is 2·97 Å.

Crumpling of the Molecules.—Inspection of $\sigma_{22}(N_2)$ in Table 2 for the C_6 compounds on either of these gas-kinetic models shows a trend in cross-section with molecular flexibility. The most rigid molecule 2 : 3-dimethylbut-2-ene has the largest cross-section, and hexa-1 : 5-diene which is the most flexible has the smallest. The same trend was observed in momentum transfer cross-section (Cummings, McCoubrey, and Ubbelohde, *loc. cit.*). Justification for applying the kinetic theory approximations used here lies in the comparative character of the method adopted. The conclusions are based essentially on the observed variations in parameters defined in a specific manner for a range of related molecules. The use of the more realistic intermolecular potential (12 : 6) for definition of the parameters gives the same general trends as are observed with the simpler rigid-sphere model, but to an even more marked degree.

The Hydrogen Effect with Flexible Molecules.—Inspection of Table 2 shows that, whatever model is used, Δ has a finite positive value for flexible molecules, which is definitely larger than for relatively stiff molecules of similar mass. In contrasting hydrogen–hydrocarbon and nitrogen–hydrocarbon collision processes, three factors may be considered as possible causes for the differences found : (1) Quantum effects may be more important with hydrogen than with nitrogen. (2) Departure from spherical symmetry of the intermolecular potential in the colliding species may lead to differences between hydrogen and nitrogen collisions with hydrocarbons. (3) The rate of transfer, reversibly, from translational to internal energy in collision between hydrogen and the flexible hydrocarbons may be markedly greater than in collisions with nitrogen.

Quantum deviations in the transport properties of systems involving hydrogen in the temperature range considered are generally assumed to be negligible (cf. Mason and Rice, *J. Chem. Phys.*, 1954, **22**, 522). This is also borne out by simple De Broglie wave-length considerations.

The effect of non-spherical symmetry of the intermolecular potential on transport properties has not yet been calculated in detail. In the comparative method adopted, effects due to the non-spherical shape of the hydrocarbon molecules should cancel out when *differences* are calculated between $\sigma(H_2)$ and $\sigma(N_2)$.

Finally, the Bryan–Pidduck model (Chapman and Cowling, *op. cit.*; Pidduck, *Proc. Roy. Soc.*, 1922, *A*, **101**, 101) provides a means of estimating the influence of inelastic collisions on transport properties. This method of calculation shows that effective transfer of energy between internal and translational degrees of freedom leads to a decrease in diffusion coefficient and effectively increases the cross-section. Moreover, ultrasonic measurements support the view that molecular flexibility markedly enhances the probability of inelastic collisions (McGrath and Ubbelohde, in the press; McCoubrey, Parke, and Ubbelohde, *Proc. Roy. Soc.*, 1954, *A*, **223**, 155). It has been known for some time that hydrogen is peculiarly effective in leading to inelastic collisions. Thus theoretical (Schwartz, Slawsky, and Herzfeld, *J. Chem. Phys.*, 1952, **20**, 1591; Takayanagi, *Progr. Theor. Phys.*, 1952, **8**, 111) and experimental work (Richards, *J. Chem. Phys.*, 1936, **4**, 561) give direct support to the view that hydrogen is extremely efficient in transferring energy on collision. From a more chemical standpoint, the exceptional efficiency of hydrogen can also be inferred from its influence on the unimolecular decomposition of

ethers (Hinshelwood, " Kinetics of Chemical Change," Oxford Univ. Press, 1949) and on the gaseous oxidation of acetaldehyde and *n*-hexane (Small and Ubbelohde, *Nature*, 1951, **168**, 201; *J. Appl. Chem.*, 1953, **3**, 193). The new findings support the view that this exceptional efficiency of hydrogen is particularly marked in collision with flexible molecules.

It is of interest to consider how the " hydrogen effect " would vary in a homologous series, starting with comparatively inflexible molecules and proceeding to molecules of greater flexibility and molecular weight. So far as the accuracy of the present method permits, once a certain degree of flexibility has been attained an asymptotic state is reached. There appears to be no marked further rise in Δ with increasing chain length.

Since each collision is localised this is perhaps to be expected. Molecular flexibility merely smears quantum restrictions in the region immediately around the collision complex. Once these have attained approximately the classical values, no further effects are to be expected with still greater increase in chain length.

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Colouring Matters of the Aphididae. Part XIV. The Course of Substitution Reactions and the Stereochemistry of the Erythroaphins.*

By B. R. Brown, A. Calderbank, A. W. Johnson, J. R. Quayle, and Sir Alexander R. Todd.

[Reprint Order No. 5754.]

The course of the interaction of erythroaphin with amines, alkaline potassium permanganate, and bromine is discussed and a stereochemical explanation offered for the conversion of erythroaphin-*sl* into derivatives of the *fb*-series observed with the first two of the above reagents but not with bromine. The arguments are extended to include the results of the Thiele acetylation of erythroaphin-*sl* where inversion does not occur and of monohydroxyerythroaphin-*sl* where it does. It is postulated that the *fb*-series have both pairs of reduced rings fused in the *cis*-configuration and that in the *sl*-series, one pair is *cis* and the other *trans*. Ultra-violet irradiation of the tetra-acetyldihydroerythroaphins-*fb* or -*sl*, as well as the penta-acetyldihydrohydroxyerythroaphins-*fb* or -*sl*, causes racemisation at the optically active centres and from the irradiation of *cis-cis*-tetra-acetyldihydroerythroaphin (*fb*-series), the *cis-trans*-isomer (*sl*-series) has been isolated as well as the hitherto unknown *trans-trans*-isomer. A consideration of the relative configuration at the four asymmetric centres leads to a complete structure for each of the isomers.

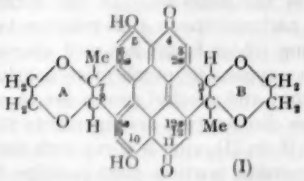
In an earlier paper (Part XIII) the alternative structures (I) and (II) were advanced for erythroaphin, the red pigment of the aphin series. Two well-defined series of aphins have been isolated from natural sources: the *fb*-series from *Aphis fabae* and several other species, and the *sl*-series from *Tuberolachnus salignus*. Strong evidence has been provided (Part XII, *J.*, 1955, 954) for the view that the two erythroaphins are stereoisomers and the relation between erythroaphin-*fb* and erythroaphin-*sl* can now be examined in the light of the basic erythroaphin structure (I).† This structure will be adopted in preference to (II) on the grounds that a plausible explanation for the course of the substitution reactions and interconversions of the isomers can be developed only on the basis of (I).

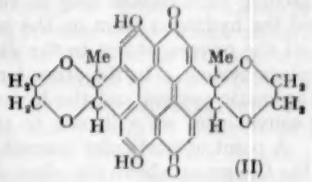
Both erythroaphins are optically active. Owing to the intense colour of their solutions, accurate measurement of their optical rotation is difficult, but by using an intense white source erythroaphin-*fb* was found to have a specific rotation of approximately +20°

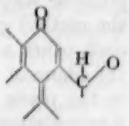
* Part XIII, *J.*, 1955, 959.

† Numbering of the complete ring system is postponed. The numerals used in the present discussion refer only to the coronene numbering shown in formula (I). Complete enumeration of the molecule awaits final clarification of the structure.

and erythroaphin-*sl* of +150° (±15°) (both in $CHCl_3$). The situation is much the same with the two diacetylerythroaphins which, in acetone, have specific rotations of approx. 0° (*fb*), and +95° (±15°) (*sl*), and the two dibromoerythroaphins which have [α] +25° (*fb*) and ÷150° (*sl*) (in $CHCl_3$), but the two tetra-acetyldihydro-derivatives, which give


(I)

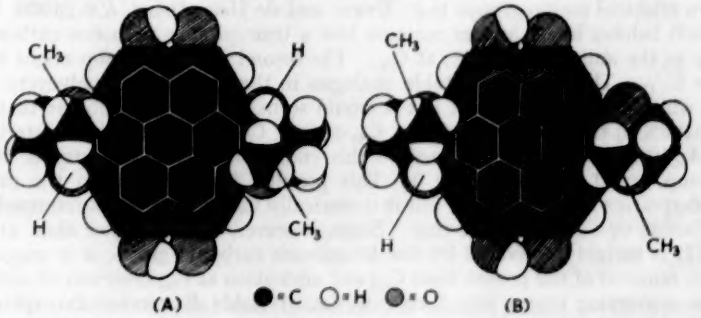

(II)


(III)

yellow solutions, are more easily studied. When freshly prepared, tetra-acetyldihydro-erythroaphin-*fb* has $[\alpha]_D$ −560° and the *sl*-isomer has $[\alpha]_D$ +95° (both in C_6H_6). Provided that light is excluded, these rotation values are independent of the method of preparation of the tetra-acetyldihydro-derivative, *e.g.*, reductive acetylation of either erythroaphin or diacetylerythroaphin with zinc and acetic anhydride or catalytic reduction of erythroaphin either in the presence of acetic anhydride or with subsequent acetylation.

In structure (I) carbon atoms 1, 2, 7, and 8 are asymmetric. The conversion of erythroaphin-*sl* into diamino- or dihydroxy-erythroaphin-*fb* (Part XII, *loc. cit.*) must therefore involve an optical inversion at one or more of these four centres. It is noteworthy that this inversion occurs as a result of chemical reactions involving reduction and re-oxidation and also the introduction of groups larger than hydrogen; the only mechanism of stereochemical change which seems reasonable is that involving a hydrogen atom or atoms attached to one or more of the four asymmetric centres, these being located in relation to the quinone carbonyl groups as in the partial structure (III). The racemisation of centres bearing hydrogen in such positions is already known in simpler quinone molecules (cf., *e.g.*, Schmidt and Ebnöther, *Helv. Chim. Acta*, 1951, **34**, 561). In the case of erythroaphin-*sl*, however, it is optical inversion and not merely racemisation which occurs, and since it always accompanies the entry of two amino- or hydroxy-groups into the molecule, the inversion would appear to be brought about by some steric consideration

FIG. 1. *Erythroaphin: (A) cis-cis-fusion of dioxan rings; (B) cis-trans-fusion of dioxan rings.*



enforced by their presence. The existence of the erythroaphins-*sl* and -*fb* as separate stable entities even under acid conditions (under alkaline conditions addition reactions occur with great rapidity) is not surprising. Although (I) is written formally as a dihydroxy-quinone, it is so strongly hydrogen bonded that it does not contain either a simple quinonoid or a dihydroxylic system (cf. infra-red spectroscopic evidence; Johnson, Quayle, Robinson, Sheppard, and Todd, Part V, *J.*, 1951, 2633) so that inversion or racemisation of centres 1, 2, 7, or 8 is unlikely to occur so easily in the erythroaphins themselves by the mechanism under discussion. In this connection it is of interest that, whereas dipiperidinoerythroaphin-*fb* is stable towards strong acids (Part VII, Brown,

Johnson, MacDonald, Quayle, and Todd, *J.*, 1952, 4928), the diacetyl derivative, in which the quinone carbonyl groups are no longer hydrogen-bonded, is hydrolysed by dilute hydrochloric acid to yield the diacetyl derivative of dihydroxyerythroaphin-*fb*.

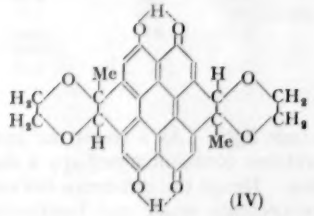
Examination of molecular models of structure (I) (Fig. 1) shows that there are two possible ways of attaching each dioxan ring to the rest of the molecule. In one form the methyl group and the hydrogen atom on the junction carbons are in a *cis*-relation to each other and one of the oxygen atoms in the dioxan ring (chair form) lies well above the plane of the perylene system. In the other form both oxygens lie much more nearly in the plane of the aromatic system and the hydrogen atom and methyl group are in a *trans*-relation. For convenience we will refer to these two dioxan ring arrangements as *cis*- and *trans*-rings. A point of particular interest is that if, in (I), ring B is *cis* with the oxygen adjacent to the CH-group above the plane of the aromatic portion, then position 3 is virtually unhindered and groups such as amino may be introduced freely, whereas there is appreciable hindrance to their introduction at 12. With ring B in the *trans*-form, however, the oxygen atoms of the dioxan ring interfere appreciably with the entry of amino-groups either at position 3 or at position 12. It is to this fact that we attribute the optical inversion which causes the change from the *sl*- to the *fb*-series in the amination and hydroxylation reactions and we formulate the reactions involved in the following way.

In erythroaphin-*fb* (IV) we consider that both A and B are "*cis*-rings," whereas, in erythroaphin-*sl* (V), ring A is a "*trans*-ring" and B a "*cis*-ring." It is clear that formula (IV) could represent either of two diastereoisomers—a *cis-syn-cis*-compound in which both angular methyl groups lie on the same side of the central perylene system and a *cis-anti-cis*-isomer in which they are opposed. Equally there could be a *cis-syn-trans*- and a *cis-anti-trans*-isomer of (V). The stereochemistry of the erythroaphins will be discussed in full later in this paper but interpretation of the interconversion reactions requires only an assumption that the disposition of the angular methyl groups relative to one another (*i.e.*, *syn* or *anti*) be the same in erythroaphin-*fb* (IV) as in erythroaphin-*sl* (V). On treatment with ammonia, reaction proceeds by the usual quinone mechanism of addition followed by reoxidation and entry of a second group by the same process. The first addition will clearly take place in such a way that the amino-group takes up a sterically unhindered position, *i.e.*, it will enter at position 3 in each case (in erythroaphin-*fb* $C_{(3)}$ is equivalent to $C_{(9)}$). On subsequent re-oxidation we assume that in accordance with the known effect of amino-groups (*e.g.*, Evans and de Heer, *Quart. Rev.*, 1950, **4**, 94) the product will behave in its further reaction like a true quinone with one carbonyl in the same ring as the amino-group, *i.e.*, at $C_{(4)}$. The second carbonyl group might be located at $C_{(10)}$ or $C_{(11)}$. There are no suitable analogies in the literature on polycyclic hydroxyquinones which bear on this point but it would seem at any rate probable that the next point of attack in the molecule would be $C_{(9)}$ or $C_{(12)}$, $C_{(9)}$ being preferred on steric grounds and the 4 : 10-quinone being assumed to this end. This being so, entry of the second amino-group would be at position 9. This position is favourable in the case of the 3-amino-derivative of the *fb*-series, but it is sterically hindered in the *sl*-intermediate (VI), being adjacent to a *trans*-dioxan ring. Since, however, the hydrogen atom attached to $C_{(8)}$ in (VI) is suitably activated by the 10-quinone carbonyl group, it is suggested that during the removal of the proton from $C_{(8)}$ and amination at $C_{(9)}$ inversion of configuration occurs, so converting ring A into a *cis*-ring, *i.e.*, it yields diamino-erythroaphin-*fb* (VII) at the second amination. It is clear that a similar explanation of the inversion and amination processes could be given if the intermediate 3-amino-quinone contained the 5 : 10-quinone system but there is as yet no direct evidence to bring to bear on this point. Likewise, whether the actual inversion process occurs during or subsequent to the entry of the second group cannot be established with certainty. Similar considerations will apply to the formation of substituted diamino-derivatives and dihydroxy-derivatives, conversion of the *sl*- into *fb*-series being uniformly observed.

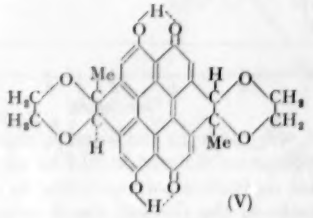
Erythroaphin-*fb* and erythroaphin-*sl* on bromination give dibromo-derivatives which are not identical, but amination of either of these derivatives yields diamino-dibromo-erythroaphin-*fb*, interconversion having occurred in the *sl*-series (Part XII, *J.*, 1955, *loc.*

cit.). These facts can also be explained on the basis of formulæ (IV) and (V). In the bromination of erythroaphin, unlike the amination, ionisation at position 2 or 8 does not occur and consequently the configuration at these asymmetric centres is retained. We may reasonably assume that the first bromine to enter the molecule will in each case do so at the unhindered position 3. Although no definite evidence is available, it seems most likely that the further action of bromine would cause substitution at position 9, giving a symmetrical structure; position 12 is a possible alternative but position 6 is most unlikely. If the dibromo-derivatives are assumed to be 3 : 9-dibromoerythroaphins, then subsequent reaction with amines would introduce amino-groups at positions 6 and 12. That an inversion should occur during this process in the case of the *sl*-isomer is not surprising, since, movement of the hydrogen atoms at the dioxan ring junctions being possible, the tendency will be for production of the configuration (*i.e.*, that of *fb*) in which steric hindrance is least.

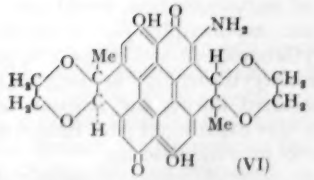
In the absence of knowledge as to the precise position of substituents in the substituted erythroaphins it is impossible to do more than advance hypothetical explanations of their interconversion. Although we have formulated both the diamino- and the dibromo-erythroaphins with the substituents in the 3 : 9-positions as though derived from intermediate 3-substituted perylene-4 : 10-quinones, spectroscopic evidence favours a 4 : 11-(or 5 : 10)-quinone structure for the acetylated disubstituted products. Despite all efforts, we have been unable to dehalogenate diaminodibromoerythroaphin-*fb* without affecting the amino-groups and so are unable to say with any certainty whether the amino-groups in that compound occupy the same positions as in diaminoerythroaphin-*fb*, or indeed whether in the latter they occupy the 3 : 9- or 3 : 12-positions. Nevertheless we consider that, on the basis of formulæ (IV) and (V) for erythroaphin-*fb* and erythroaphin-*sl*, and assuming that diaminoerythroaphin-*fb* is (VII), a reasonable explanation of the observed facts can be given, and that, as above indicated, the properties of the dibromoerythroaphins may also be explained.



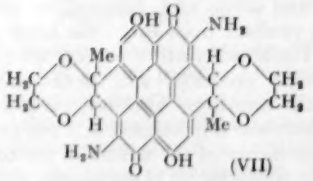
(IV)



(V)



(VI)



(VII)

It may be pointed out that the stereochemical relation of the erythroaphins-*fb* and -*sl*, *i.e.*, *cis-cis* and *cis-trans* respectively, has been deduced independently on the bases of the quantitative acetaldehyde production (Part XIII, preceding paper) and also in the present paper from conditions of the addition reactions which bring about the inversion of erythroaphin-*sl*.

On our hypothesis outlined above, the two erythroaphins should yield distinct mono-amino- and monohydroxy-derivatives since optical inversion should occur only upon the entry of a second substituent. Unfortunately we have never been able to halt reaction with ammonia or amines at the monosubstituted stage, but monohydroxy-derivatives are accessible by means of the Thiele acetylation procedure followed by hydrolysis and aerial oxidation of the initially formed penta-acetyldihydrohydroxyerythroaphins. In the

original work, it was observed that hydroxyerythroaphin-*fb* and -*sl* were extremely alike but always showed a slight difference in their infra-red absorption spectra (Part XII, *loc. cit.*). Although on this basis they were adjudged to be distinct substances, the puzzling observation was made that treatment with zinc dust and acetic acid converted both of them in rather poor yield into a product identified by infra-red spectrum as erythroaphin-*fb*, although reduction alone had never previously been known to convert a member of the *sl*-series into an *fb*-derivative. Subsequent work on the penta-acetyldihydrohydroxyerythroaphins has helped to remove this apparent anomaly. It was found that the optical rotations of the freshly prepared *fb*- and *sl*-derivatives differed considerably ($[\alpha]_D$ −230° and −40° respectively) but that solutions exhibited a very ready mutarotation in the presence of light. The change in rotation was greatly accelerated when the solutions were irradiated and both penta-acetyldihydro-compounds yield, at equilibrium (after *ca.* 24 hours), solutions of substantially the same rotation (−30°). The penta-acetyl derivatives are unfortunately rather unstable and no pure compounds have been isolated from the solution after equilibration by irradiation. Nevertheless it seems clear that the effect of light is to cause racemisation at one or more of the asymmetric centres and thus an explanation is provided for the anomaly presented by the hydroxyerythroaphins. The process of preparing them lasts several days and no

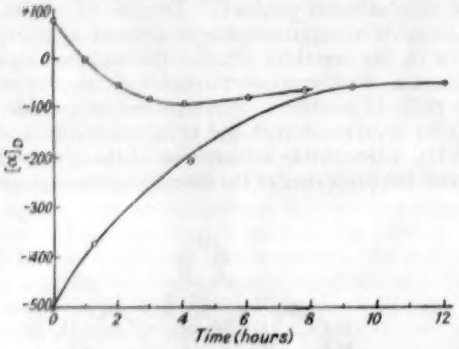


FIG. 2. *Effect of ultra-violet irradiation on the optical rotation of benzene solutions of the tetra-acetyldihydroerythroaphins-*fb *and* -sl.

effort was made in the original experiments to exclude light. As a result the hydroxyerythroaphins isolated would be expected to be mixtures containing perhaps a majority of that derivative corresponding to the original aphin. Hence the difference between the products in the *fb*- and the *sl*-series would be unexpectedly small, and treatment with zinc and acetic acid, followed by normal processes of recrystallisation, would give, as the final product from each, the least soluble aphin, *viz.*, erythroaphin-*fb*. A repetition of the Thiele acetylation process with the hydroxyerythroaphin-*fb* and -*sl* gave apparently identical products, *i.e.*, hexa-acetyldihydrodihydroxyerythroaphin, as judged by the optical rotations, but extensive decomposition occurred during the reaction and the product was not isolated in a pure state. However, this experiment gave further support to the theory of the nature of the conversion of the *sl*- into the *fb*-series.

In following up observations that samples of tetra-acetyldihydroerythroaphin-*sl* sometimes varied considerably in their optical rotation, it was discovered that solutions both of this substance and of the corresponding *fb*-derivative also exhibit mutarotation in the presence of light. The change in rotation was markedly slower than in the case of the penta-acetyldihydrohydroxyerythroaphins and the compounds were themselves more stable, so that the tetra-acetyldihydroerythroaphin series was more convenient for a study of the nature of the mutarotation. As before, the change was slow in diffused daylight but much more rapid when the solutions were irradiated with ultra-violet light, both isomers yielding, at equilibrium, solutions with substantially the same optical rotation (*ca.* −50°; Fig. 2), although the *sl*-isomer attained the equilibrium value appreciably more rapidly than the *fb*-isomer. It is of interest to consider these observations in the light of the proposed structures (IV) and (V) for erythroaphin-*fb* and -*sl*. In the

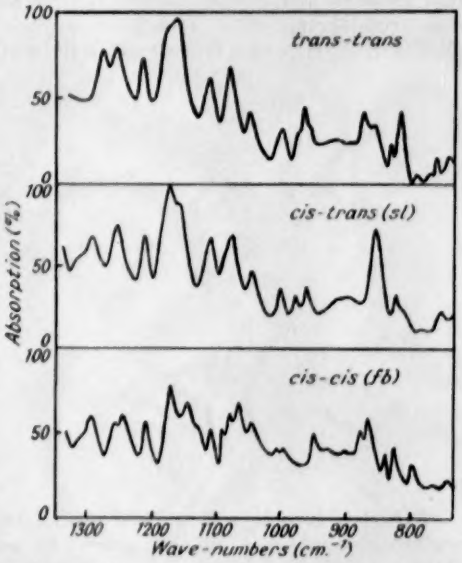
unsubstituted erythroaphins, or in the tetra-acetyldihydro-derivatives, there is no steric factor to impose inversion rather than racemisation at the asymmetric centres. We would therefore assume that the effect of ultra-violet irradiation would be to cause racemisation at positions 2 and 8 in each case. This, because of the symmetry of the molecule, would lead to the production of three diastereoisomers corresponding to erythroaphins-*fb*, -*sl*, and a third erythroaphin in which both A and B are "*trans*-rings." Tetra-acetyldihydroerythroaphin-*fb* (the least soluble component), as well as unchanged *sl*-isomer, has been isolated from the equilibrium mixture prepared by irradiation of tetra-acetyldihydroerythroaphin-*sl* and when, in a larger-scale experiment, tetra-acetyldihydroerythroaphin-*fb* (*cis-cis*) was irradiated with ultra-violet light, there was isolated from the more soluble fractions not only the *sl*(*cis-trans*)-isomer but also the hitherto unknown *trans-trans*-isomer. Hydrolysis of the *trans-trans*-tetra-acetyldihydro-compound ($[\alpha]_D$ +380°) gave the corresponding *trans-trans*-erythroaphin which, as yet,

TABLE.

Bands in the 1000—800 *cm.*$^{-1}$ *region in the infra-red spectra of the three isomers of erythroaphin.*

cis-cis (*fb*)	*cis-trans* (*sl*)	*trans-trans*
952	974	964
878	955	870
864	852	829 (weak)
842	818	813
830		
805		

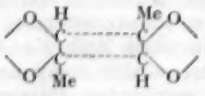
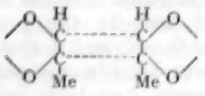
FIG. 3. *Infra-red spectra of the erythroaphin isomers.*



has not been isolated from any species of aphid. It is more soluble in organic solvents than the others and when examined in a white light has a high positive rotation ($[\alpha]$ +325°). There is thus a gradation of physical properties, especially solubilities and optical rotation, from the least soluble tetra-acetyldihydroerythroaphin-*fb* with a negative rotation through the *sl*-isomer to the most soluble *trans-trans*-isomer with a high positive rotation. Apart from differences in optical rotation, the three erythroaphins can be distinguished by their infra-red spectra (Fig. 3), particularly in the 1000—800 cm.$^{-1}$ region (see Table above).

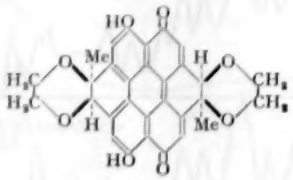
As all three of the isomers of erythroaphin are optically active, a reconsideration of structures (I) and (II) makes it possible to eliminate certain of the stereochemical isomers on the grounds of symmetry. In the aromatic portion of the molecule either of the hydrogen atoms of the two hydroxyl groups is almost symmetrically placed with regard to the carbonyl and hydroxyl oxygen atoms. The energy involved in the transfer of hydrogen from one oxygen to the other is relatively small and a state of dynamic equilibrium is assumed in the *peri*-hydroxy-quinone system. Consequently this system will not of itself confer asymmetry on the molecule and for the purpose of stereochemical considerations the perylene system can be ignored, leaving the groups (VIII) or (IX),

depending on whether the angular methyl groups are situated at positions 1 and 7 or at positions 1 and 8. The situation thus obtained recalls that of the truxinic and truxillic acids except that the four asymmetric carbon atoms are arranged as a rectangle rather

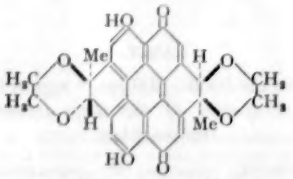
(VIII)   (IX)

than a square. In (VIII), an arrangement with the methyl groups in the *trans*-position relative to each other (*anti*-forms) can be eliminated because both the *cis-cis*- and *trans-trans*-erythroaphin isomers would then have a centre of symmetry. Hence on the basis of (VIII), the structures (X) and (XI), *i.e.*, with the methyl groups in the *cis*-position relative to each other (*syn*-forms), must represent erythroaphin-*fb* and -*sl* respectively.

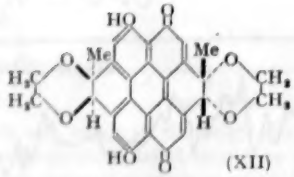
From what has been said previously, structure (I) is preferred to (II) for erythroaphin but it should be noted that if the angular methyl groups are arranged as in (II) (or IX) they must be in the *trans*-position relative to each other; otherwise *cis-cis*- and *trans-trans*-erythroaphin would each have a plane of symmetry. On this basis structures (XII) and (XIII) would be assigned to the erythroaphins-*fb* and -*sl* respectively.



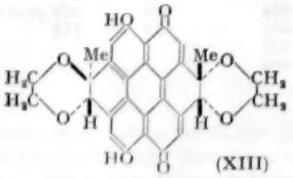
(X) (*cis-syn-cis*)



(XI) (*anti-syn-cis*)



(XII)



(XIII)

Experiments designed to show the relative positions of the methyl groups in the erythroaphin molecule and thus remove all ambiguity as to the complete stereochemical structure of all three isomers, are at present in progress.

Experimental

Dibenzoylerythroaphin-sl.—To erythroaphin-*sl* (55 mg.), dissolved in dry pyridine (6 c.c.), at <10° benzoyl chloride (1·0 c.c.) was added dropwise with shaking. The mixture was allowed to warm to room temperature and kept for a further 15 min. with occasional shaking; then the orange solution was diluted with ether (30 c.c.) and poured on ice. The ethereal layer was separated, washed, dried, and concentrated (to 5 c.c.), and then heated on the steam-bath for 5 min. with ethanol (20 c.c.) in order to convert the residual benzoyl chloride into ethyl benzoate. After cooling, the product separated as orange crystals which were collected, washed with ethanol, and dried (60 mg.). It was recrystallised from a mixture of benzene (3 c.c.) and light petroleum (b. p. 40—60°; 15 c.c.) and further purified by chromatography in benzene (3 c.c.) on silica (7 × 2 cm.). The column was eluted with benzene–acetone (20 : 1), and the orange band collected. The eluate (300 c.c.) was concentrated (to 4 c.c.), diluted with hot light petroleum (b. p. 40—60°; 10 c.c.), and cooled, the *dibenzoate* (32 mg.) being obtained as orange nodules. For analysis it was dried at 105°/0·2 mm. overnight (Found: C, 73·1; H, 4·3. $C_{44}H_{30}O_{10}$ requires C, 73·5; H, 4·2%). Light absorption in $CHCl_3$: max. at 489, 487, 430, 350, and 332 mμ (log ε 3·84, 3·83, 4·59, 4·03, 4·03, and 4·20 respectively). The compound

was very soluble in chloroform and ether, soluble in ethoxyethanol and cold benzene, slightly soluble in ethanol, and insoluble in light petroleum. It charred between 220° and 230° but had no definite m. p. The infra-red spectrum (Nujol mull) showed maxima at 1754, 1645, 1623, 1605, 1565, 1366, 1307, 1292, 1235, 1212, 1190, 1172, 1144, 1111, 1096, 1073, 1053, 1014, 962, 870, 840, 825, 800, 763, 719, 714, 704, and 696 cm.$^{-1}$.

Diacetyldihydroxyerythroaphin-fb.—Dipiperidinoerythroaphin-*fb* (53 mg.; from erythroaphin-*sl*; Part XII, *loc. cit.*) was dissolved in dry pyridine (7·5 c.c.) and acetylated by the addition, dropwise, of acetyl chloride (0·8 c.c.), the temperature being kept below 10°. After a further 15 min. at room temperature the solution was poured into ice-cold 3N-hydrochloric acid (50 c.c.) and after 3 min. the precipitated product was extracted into benzene (3 × 15 c.c.). The combined benzene extracts were washed with N-hydrochloric acid, then water, dried, and concentrated (to 5 c.c.). The orange-coloured solution, which contained a mixture of acetylated dipiperidinoerythroaphin-*fb* and acetylated dihydroxyerythroaphin-*fb*, was filtered and the warm filtrate diluted with light petroleum (10 c.c.; b. p. 40—60°). After slow cooling, orange crystals of *diacetyldihydroxyerythroaphin*-fb were obtained which were separated, washed, and dried (30 mg.) (Found, in a sample dried at 90°/10^{-3} mm. for 5 hr.: C, 65·4; H, 4·5. $C_{24}H_{26}O_{12}$ requires C, 65·2; H, 4·2%). Light absorption in $CHCl_3$: max. at 433, 349, 332, 320, 282, and 256 mμ (log ε 4·55, 3·93, 3·96, 4·08, 4·01, and 4·36 respectively). The infra-red spectrum, determined as a mull in Nujol, showed maxima at 3333, 1786, 1647, 1605, 1562, 1506, 1366, 1311, 1274, 1176, 1153, 1133, 1098, 1079, 1047, 980, 948, 935, 917, 904, 885, 864, 828, 803, 777, 760, 738, and 687 cm.$^{-1}$. Hydrolysis of the product in chloroform with 2N-sodium hydroxide at room temperature gave a red solution which showed the characteristic absorption maxima of dihydroxyerythroaphin-*fb* (hand spectroscope: max. at 596, 567, 526, and 450 mμ). The filtrate from the preparation of diacetyldihydroxyerythroaphin-*fb* was shaken with 50% hydrochloric acid which extracted the coloured material, and the acid extract was diluted with twice its volume of water and the product re-extracted into benzene The solution then showed the absorption maxima of dipiperidinoerythroaphin-*fb* (hand spectroscope: max. at 610, 574, 530, and *ca.* 450 mμ).

Irradiation of Tetra-acetyldihydroerythroaphin-sl. *Isolation of the* fb-*Isomer.*—Tetra-acetyldihydroerythroaphin-*sl* (500 mg.; $[\alpha]_D$ +35°; all rotations determined in C_6H_6) was dissolved in benzene (400 c.c.) and irradiated with ultra-violet light (λ 300—365 mμ) for 5 hr. The dark orange solution ($[\alpha]_D$ −48°) was concentrated (to 15 c.c.) *in vacuo* and chromatographed on a column of silica (9 × 5 cm.), elution being with benzene–acetone (20 : 1). The yellow-orange eluate was concentrated (to 50 c.c.), diluted with light petroleum (b. p. 40—60°; 200 c.c.), and kept for two days with exclusion of light. The crystalline product (268 mg.; $[\alpha]_D$ −170°) was separated and repeatedly recrystallised from benzene–light petroleum. The specific rotation of the product gradually approached that of the *fb*-isomer and after five such crystallisations the tetra-acetyl derivative (88 mg.) had $[\alpha]_D$ −435°. This product (73 mg.) was dissolved in chloroform (35 c.c.) and was shaken for 1 min. with a solution of aqueous sodium hydroxide (4 c.c. of 10%) in methanol (30 c.c.). The green suspension of the sodium salt of erythroaphin was acidified with dilute hydrochloric acid, and the red chloroform layer separated and washed with water and sodium hydrogen carbonate solution. The chloroform solution was dried and concentrated, and the erythroaphin (30 mg.) caused to crystallise (as dark red needles) by the addition of hot ethanol. It was separated, recrystallised from chloroform–ethanol, and then dried at 120°/1·5 mm. for 6 hr. The ultra-violet and infra-red absorption spectra of the product (25 mg.) were identical with those of erythroaphin-*fb*.

The combined mother-liquors from the benzene–light petroleum crystallisations of the irradiated product was kept for 4 weeks at room temperature in the dark. A second crop of crystals (50 mg.; $[\alpha]_D$ −230°) were removed and the mother-liquors concentrated (to 20 c.c.) and then diluted with light petroleum (90 c.c.). After several hours in the dark, a crystalline product (100 mg.) separated which had $[\alpha]_D$ +40°. Hydrolysis of this tetra-acetyl compound (75 mg.) by the procedure outlined above gave an erythroaphin (33 mg.) which recrystallised from chloroform–ethanol to give a product (25 mg.) as small dark red needles. It was dried at 100°/5 mm. for 12 hr. and the infra-red spectrum determined which was identical with that of erythroaphin-*sl*.

Irradiation of Tetra-acetyldihydroerythroaphin-fb. *Isolation of the* sl- *and the* trans-trans-*Isomer.*—Tetra-acetyldihydroerythroaphin-*fb* (685 mg.) was dissolved in purified dry benzene (800 c.c.) in an atmosphere of nitrogen, the yellow solution having $[\alpha]_D$ −565°. (All specific rotation values on the tetra-acetyldihydroerythroaphins were determined in benzene solution.) It was placed in a silica flask and irradiated with ultra-violet light (λ 300—365 mμ) for 18 hr.

after which the orange-red solution had $[\alpha]_D$ −300°. It was concentrated (to 100 c.c.) under reduced pressure, brought on a column (10 × 5 cm.) of silica, and eluted with benzene. The orange eluate was concentrated (to 100 c.c.), an equal volume of light petroleum added, and the solution kept for three days with exclusion of light. The orange crystals (495 mg.) formed were separated and the mother-liquors stored in a dark cupboard. The crystals were dissolved in benzene, giving a solution with $[\alpha]_D$ −470°, which was irradiated for 20 hr; the rotation was then $[\alpha]_D$ −180°. The purification was effected as before (giving 300 mg. of $[\alpha]_D$ −380°), the mother-liquors being set on one side and the crystals dissolved in benzene and again irradiated (to $[\alpha]_D$ −160°). Chromatography of the resulting solution gave a main fraction from which a crystalline product (235 mg.; $[\alpha]_D$ −355°) was obtained. Further crystallisations gave successive crops (185 mg. of $[\alpha]_D$ −480°; then 84 mg. of $[\alpha]_D$ −520°). The final product which formed orange nodules was identical with the original tetra-acetyldihydroerythroaphin-*fb*. Hydrolysis with methanolic sodium hydroxide as before gave erythroaphin-*fb* (26 mg. from 70 mg. of tetra-acetyl derivative), the infra-red spectrum of which was identical with that of an authentic specimen.

The four batches of benzene–light petroleum mother-liquors from the three irradiation experiments and the first of the subsequent crystallisations were combined and kept at room temperature for one week with exclusion of light. All operations from this stage onwards were carried out in subdued light or with total exclusion of light. The small amount of crystalline material which had separated was removed by filtration and the solution concentrated (to 100 c.c.) under reduced pressure. It was diluted with an equal volume of light petroleum and kept for three days. A further small amount of crystalline material was separated and the mother-liquors were concentrated (to 20 c.c.), diluted with light petroleum (80 c.c.), and kept in the dark overnight. The orange-brown crystals (32 mg.; A) were separated, and the mother-liquors concentrated (to 5 c.c.) and diluted with light petroleum (60 c.c.), more crystals (88 mg.; B) being obtained overnight. By further concentration (to 3 c.c.) of the mother-liquors, dilution with light petroleum (40 c.c.) and keeping in the dark for three weeks, another crop of heavy brown nodules (70 mg.; C) was obtained. Repetition of this process gave a small quantity of a dark brown powder (10 mg.; D) after one week. All of the fractions A, B, C, and D showed the typical visible-light absorption spectrum of tetra-acetyldihydro-erythroaphin with prominent bands at 467 and 502 mμ (hand-spectroscope).

Fraction A (30 mg.; $[\alpha]_D$ +20°) was hydrolysed with methanolic sodium hydroxide to give an erythroaphin (8 mg.), the infra-red spectrum of which showed the main characteristics of erythroaphin-*sl*.

Fraction C (70 mg.; $[\alpha]_D$ +380°) was more soluble in benzene than the *fb*- or *sl*-isomer. It was hydrolysed as before with methanolic sodium hydroxide, and the erythroaphin purified by partition between chloroform and sulphuric acid of various strengths (Part III, *J.*, 1950, 485). After crystallisation of the product from chloroform–ethanol, the trans-trans-*isomer* was obtained as dark red crystals (22 mg.), m. p. 240—242° with previous darkening, $[\alpha]$ +325° (in $CHCl_3$; white light) (Found: C, 70·5; H, 4·0. $C_{20}H_{22}O_6$ requires C, 70·6; H, 4·3%). Light absorption in $CHCl_3$: max. at 589, 564, 523, 486, 448, 422, and 254 mμ (log ε 3·80, 4·17, 3·99, 3·70, 4·46, 4·35, and 4·46 respectively). The infra-red spectrum determined on a mull in Nujol showed maxima at 667, 691, 722, 741, 763, 789, 813, 829, 855, 870, 964, 1000, 1047, 1076, 1111, 1164, 1183, 1212, 1255, 1279, 1346, 1587, and 1626 $cm.^{-1}$.

Fraction C (88 mg.; $[\alpha]_D$ +185°) was converted into the corresponding erythroaphin which was purified by the sulphuric acid method and crystallised from chloroform–ethanol as before. The product (17 mg.; $[\alpha]_D$ +190°) appeared from the infra-red spectrum to be a mixture of the *sl*- and the *trans-trans*-isomer.

Penta-acetyldihydrohydroxyerythroaphin-fb.—Erythroaphin-*fb* (100 mg.) was treated with acetic anhydride and perchloric acid by the method described in Part VII (*loc. cit.*). The ethereal extract of the product was washed with 1% hydrochloric acid and then with 0·5% aqueous sodium hydroxide and dried. After removal of solvent, the residue was dissolved in benzene (10 c.c.), brought on a column of silica (9 × 3 cm.), and eluted with benzene. The deep yellow benzene eluate was concentrated to small bulk (1 c.c.), diluted with light petroleum, and kept overnight. The precipitated brown solid (22 mg.) was separated, redissolved in benzene (0·5 c.c.), and again obtained as a non-crystalline powder by addition of light petroleum (3 c.c.). For analysis it was dried at 120°/0·5 mm. for 8 hr. (Found: C, 64·8; H, 4·3. $C_{40}H_{34}O_{14}$ requires C, 65·0; H, 4·6%). This *compound* was very soluble in benzene, acetone, chloroform, ethanol, and ethyl acetate.

In another experiment, erythroaphin-*fb* (50 mg.) was dissolved in "AnalaR" acetic

anhydride (8 c.c.) containing perchloric acid (1 drop of 60%) and kept at 0° for 24 hr. The reaction, as well as the subsequent purification, were carried out with exclusion of light. Excess of anhydride was hydrolysed by shaking the mixture with saturated aqueous sodium acetate (32 c.c.) at 0° for 30 min. The product was extracted with ether (50 c.c.), and the extract washed successively with 1% hydrochloric acid (3 × 50 c.c.), saturated sodium hydrogen carbonate solution (2 × 50 c.c.), 1% sodium hydroxide solution (4 × 30 c.c.), alkaline sodium dithionite solution (2 × 30 c.c.), and water (2 × 50 c.c.), and the resulting bright yellow ethereal solution was dried. The optical rotation was measured ($[\alpha]_D$ −230°) and the solution in the polarimeter tube irradiated with a tungsten lamp. After 12 hr. the rotation had fallen to $[\alpha]_D$ −130° and after 24 hr. to $[\alpha]_D$ −30°. The concentration (45 mg./100 c.c.) was estimated by measurement of the optical density at 496 mμ in chloroform solution.

In another experiment penta-acetyldihydrohydroxyerythroaphin-*sl* was prepared, also with exclusion of light as described above. The optical rotation of the ethereal solution (26 mg./100 c.c.) which initially was $[\alpha]_D$ −40° changed to $[\alpha]_D$ −30° after irradiation with a tungsten lamp for 24 hr. The combined irradiated solutions were evaporated and the residue was dissolved in benzene and chromatographed on a column of silica. The benzene eluate showed maxima at 490, 457, 430, and 407 mμ, as did the original solutions before irradiation. Evaporation of the benzene solution caused extensive decomposition.

Hexa-acetyldihydrodihydroxyerythroaphin.—Both hydroxyerythroaphin-*fb* and -*sl* were treated with acetic anhydride and perchloric acid with exclusion of light by the method described in the previous paragraphs. Extensive decomposition occurred during the reaction but the ethereal solutions of the products were irradiated as before with a tungsten lamp. The optical rotations of both solutions were zero both before and after irradiation. Attempted isolation of the product merely resulted in decomposition.

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Studies on Biological Methylation. Part XV. The Formation of Dimethyl Selenide in Mould Cultures in Presence of* D- *and* L-*Methionine, or of Thetins, All containing the* $^{14}CH_3$ *Group.*

By PHILIP B. DRANSFIELD and FREDERICK CHALLENGER.

[Reprint Order No. 5829.]

D- and L-Methionine (as also DL-methionine; Part XIV *) labelled with $^{14}CH_3$, in cultures of *Aspergillus niger* containing selenate, give radioactive dimethyl selenide, the methylation percentage being 90—100. This figure is reduced to 53—61 when labelled D-methionine competes with an equal weight of unlabelled L-isomer in the same culture, and *vice versa*. The two stereoisomers appear to be equally available as methyl donors. Dimethylacetothetin and dimethyl-β-propiothetin chloride are not direct methyl donors and are very poor methyl sources. The availability of *S*-methyl-DL-methioninesulphonium iodide, labelled in one methyl group, as a methyl source has been examined.

In *A. niger* cultures containing labelled methionine about one-third of the radioactivity appears as an acid which contains sulphur but no keto- or amino-group.

CHALLENGER, LISLE, and DRANSFIELD (Part XIV *) found that methionine is the most important source of methyl groups in the production of dimethyl selenide or trimethylarsine by *Scopulariopsis brevicaulis* and of dimethyl selenide by *Aspergillus niger*. Betaine, choline, and formate are of secondary importance and probably act mainly as methyl sources in the synthesis of methionine. Dimethylacetothetin chloride $Cl^-\{Me_2S^+\cdot CH_2\cdot CO_2H$

* Part XIV, *J.*, 1954, 1760.

and dimethyl-β-propiothetin chloride $Cl^-\{Me_2S^+\cdot CH_2\cdot CH_2\cdot CO_2H$ are not direct methyl donors in *A. niger* cultures, but their significance as methyl sources was not assessed. A similar experiment showed that *S*-methyl DL-methioninesulphonium iodide, $Cl^-\{Me_2S^+\cdot CH_2\cdot CH_2\cdot CH(NH_2)\cdot CO_2H$, though probably not a direct methyl donor to selenium, was probably an effective source of methionine, (*a*) by loss of one methyl group partly as carbon dioxide (see Table 2) and (*b*) by transfer of this methyl to homocysteine, possibly as an oxidised fragment. These results and those of workers with higher plants and animals (see Part XIV) suggest that methionine occupies a key position as a methyl donor, and in animals is probably first converted into *S*-adenosinylmethionine (Cantoni, *J. Biol. Chem.*, 1953, **204**, 403).

Cantoni (*ibid.*, 1951, **189**, 208, 211) found that L-methionine is twice as active as the DL-isomer in the methylation of nicotinamide to *N'*-methylnicotinamide by the enzyme nicotinamide methyl kinase. This system involves the formation of *S*-adenosinylmethionine (see Part XIV for references to Cantoni's work, and also Baddiley and Jamieson, *Chem. and Ind.*, 1954, 375). Cantoni concludes that D-methionine is inactive as a methyl donor in this system. Betaine and dimethylacetothetin were also inactive but, in presence of DL-homocysteine, methylation of nicotinamide occurred readily. Betaine is 2—5 times more effective as a methyl donor to selenium in *A. niger* cultures in presence of homocysteine (Part XIV). Cantoni's result with dimethylacetothetin agrees with our own (see pp. 1156, 1160), but we have not studied the behaviour of the thetins in presence of added homocysteine.

Handler and Bernheim (*J. Biol. Chem.*, 1943, **150**, 335) found that L-methionine was twice as effective as the D-isomer in the methylation of guanidinoacetic acid to creatine by rat liver slices. However, the α-keto-acid, $MeS\cdot CH_2\cdot CH_2\cdot CO\cdot CO_2H$ was as effective as L-methionine itself. Possibly D-methionine is converted through the keto-acid into the L-amino-acid before transmethylation occurs : this is supported by the observation that transmethylation from D-methionine did not take place in the presence of benzoic acid, a D-amino-acid oxidase inhibitor.

We have now studied the relative utilisation of D- and L-methionine in the mycological methylation of sodium selenate, giving dimethyl selenide. The results (see Expts. 1—4, Table 1) show that D-methionine is quite as effective as L- or DL-methionine.

In the liquid medium used in these experiments the total amount of sulphate present per culture is 0·67 mmole. Hence the maximum amount of " natural methionine " which the mould could synthesise is only 0·67 mmole per culture, which is small compared with 2 mmole of methionine added to each culture. The actual amount of natural methionine formed is probably much less. A rough estimate of this can be made from our experimental figures. If we assume methionine to be the only direct methyl donor present and a maximum theoretical methylation of 100%, then, from the average figure of 95% methylation for the earlier stages of the experiment obtained by adding 2 mmoles of radioactive L-methionine to the culture, we can calculate that $2(100—95)/95 = \sim 0{\cdot}1$ mmole of " natural methionine " is actually formed from sulphate in the medium.

If this small amount of " natural methionine " is always present in the culture at the time of addition of the 2 mmoles of radioactive methionine, there would be present twenty times as much radioactive as non-radioactive " natural " methionine. If the amount of radioactive methionine added was halved, this ratio would be 10 : 1 and there would be approximately 90% methylation. Clearly, under these experimental conditions such a large excess of radioactive methionine is being added that if D-methionine were, say, only half as effective as the L-enantiomorph, the amount of methylation would be only 5% less, *i.e.*, 90 instead of 95%. Consequently experiments (p. 1157) were set up in which equal amounts of D-[*Me*-^{14}C]methionine and non-radioactive L-methionine were added to the selenate cultures. Since absolute values for amount of methylation were not known, owing to uncertainties such as the magnitude of the " back-scatter " correction for mercuri-chloride precipitates (see p. 1156), a similar set of experiments (Table 1, Expts. 5—7) employing radioactive L- and non-radioactive D-methionine was carried out simultaneously. The results showed that the L- and the D-enantiomorph of methionine are utilised with equal facility in mycological methylations. This agrees with the results of work on the

utilisation of D- and L-methionine for the growth of rats (Jackson and Block *J. Biol. Chem.*, 1937, **122**, 425; Rose, *Physiol. Rev.*, 1938, **18**, 109; Bach, "The Metabolism of Protein Constituents in the Mammalian Body," Clarendon Press, Oxford, 1952, p. 161). It seems that (*a*) the methyl group of D-methionine *as such* is labile in mould cultures, or (*b*) if D-methionine cannot be utilised then it must be converted in the mould cell into the L-form as rapidly as the competing L-methionine can be utilised, or (*c*) that both processes (*a*) or (*b*) occur simultaneously. Information from other sources can be found in support of each of these possibilities. Horowitz (*J. Biol. Chem.*, 1944, **154**, 141) found by the Warburg technique that a D-amino-acid oxidase obtained from the mould *Neurospora crassa* (wild, *i.e.*, normal type) deaminates many DL-amino-acids, and DL-methionine most rapidly of all. In this case γ-methylthio-α-oxobutyric acid was isolated from the medium as its 2 : 4-dinitrophenylhydrazone. When L-methionine was used no oxidation occurred. A mutant strain of *N. crassa* which cannot synthesis methionine (methionine-deficient) also utilises D-methionine. Horowitz concludes that the requirements of this mutant strain for L-methionine are met by oxidative deamination of the D-isomer to the keto-acid, followed by re-amination to the L-form (alternative *b*). Unlike the D-amino-acid oxidase presumably present in Handler and Bernheim's enzyme system (see p. 1154), Horowitz's D-amino-acid oxidase is not inhibited by benzoic acid. It resembles a D-amino-acid oxidase from kidney and liver which also oxidises DL-methionine more readily than any other DL-amino-acid (Krebs, *Biochem. J.*, 1935, **29**, 1620). Rydon (*Biochem. Soc. Symposia*, 1948, **1**, 40) states that the D-forms of some amino-acids can probably be used directly in certain enzyme reactions, depending upon the points of attack and attachment. Consequently possibility (*a*) (see above) must not be overlooked since, in the interaction of adenosine triphosphate with methionine to form "active methionine" (*S*-adenosinylmethionine), only the sulphur atom of the amino-acid is involved and this is separated by two carbon atoms from the centre of asymmetry. Cantoni, however, regards D-methionine as inactive in the methylation of nicotinamide by the liver enzymes. Whether D-methionine can form an *S*-adenosinyl derivative under biological conditions is not known, nor has it yet been shown that "active methionine" is concerned in plant methylation. Nevertheless, the isolation of 5′-deoxy-5′-methylthioadenosine ("adenine thiomethyl pentoside" $C_5H_4N_5 \cdot C_4H_5O_3 \cdot CH_2 \cdot SMe$, which is a hydrolysis product of Cantoni's *S*-adenosinylmethionine) from yeast (Mandel and Dunham, *J. Biol. Chem.*, 1912, **11**, 85; Suzuki, Odake, and Mori, *Biochem. Z.*, 1924, **154**, 278), suggests that the significance of *S*-adenosinylmethionine is not confined to animals.

Horowitz remarks that (in 1944) the occurrence of D-amino-acid oxidase in fungi had not previously been recorded. It appears from our experiments that it may be present in *A. niger*.

Though it is clear that D-methionine is utilised as readily as L-methionine in the mycological methylation of selenium, the mechanism of the process has not been determined.

In experiments with liquid cultures containing radioactive L-, D-, or DL-methionine 30—50% of the added radioactivity was always found in what appeared to be a single acid. By the use of ion-exchange resins a very small quantity of this acid was isolated as an oil. It appeared from its behaviour on a paper chromatogram to be almost pure. It contained sulphur but no keto-group, and the ninhydrin reaction was negative. It was presumably a degradation product of methionine.

Obvious possibilities, such as β-methylthiopropionic acid $MeS \cdot CH_2 \cdot CH_2 \cdot CO_2H$, and methylthioacetic acid $MeS \cdot CH_2 \cdot CO_2H$ and its sulphone, were excluded by chromatographic comparisons with authentic compounds. The acid was formed early in the experiments, and accompanied by a large quantity of other acids (produced by *A. niger* from the sucrose of the medium) which disappeared later. No further degradation of this acid took place till most other food sources were exhausted. The remainder of the radioactivity then appeared as $^{14}CO_2$. Figures for methylation percentage were low even before this unknown acid was attacked, so probably it does not possess a labile methyl group. Its investigation is being continued.

It was concluded (Part XIV) that dimethylacetothetin chloride (I), dimethyl-β-propiothetin chloride (II), and probably *S*-methyl-DL-methioninesulphonium iodide (III) are not

direct methyl donors in mycological methylation. These compounds, labelled with ^{14}C in one methyl group were prepared (see Ferger and du Vigneaud, *J. Biol. Chem.*, 1950, **185**, 54, for the first two) and their significance as methyl sources studied. Methylmethioninesulphonium iodide proved to be a good source of methyl groups in the formation of dimethyl

$Cl^-\{Me_2S^+\cdot CH_2\cdot CO_2H$ (I) $\quad Cl^-\{Me_2S^+\cdot CH_2\cdot CH_2\cdot CO_2H$ (II) $\quad I^-\{Me_2S^+\cdot CH_2\cdot CH_2\cdot CH(NH_2)\cdot CO_2H$ (III)

selenide by *A. niger* (see Table 2). This agrees with the observation that it can replace methionine in the diet of white rats (Bennett, *ibid.*, 1941, **141**, 573; Handler and Benheim, *ibid.*, 1943, **150**, 335). The aceto- and propio-thetin (I and II) were very ineffective under the same conditions. Since choline also is a poor methyl source for selenium in *A. niger* cultures under certain conditions (Part XIV), it was decided to study the behaviour of thetins as methyl sources in bread–selenate cultures of *S. brevicaulis*. The results (Table 3) show that under these conditions thetins cannot be utilised as methyl sources, even to the same extent as betaine, choline, or formate. Hence the " thetin transmethylase " found in rat liver preparations by Borsook and Dubnoff (*J. Biol. Chem.*, 1948, **176**, 789) is presumably not present in the moulds *A. niger* or *S. brevicaulis* under our conditions. Du Vigneaud (Harvey Lectures, 1942—43, **38**, 39) and Maw and du Vigneaud (*J. Biol. Chem.*, 1948, **174**, 381) found that (I) and (II) are as effective as choline as sources of methyl groups for the growth of rats. Borsook and Dubnoff (*loc. cit.*) and du Vigneaud (" A Trail of Research," Cornell Univ. Press, Ithaca, 1952, pp. 102—104) found thetins effective methyl sources for the methylation of homocysteine to methionine in rat tissue prepartions or in intact rats respectively.

Du Vigneaud showed that 27% of the methyl groups of dimethylacetothetin and dimethyl-β-propiothetin was oxidised to carbon dioxide in the rat. We find that oxidation of the methyl groups of these three sulphonium compounds is much less than that of the methyl groups in betaine under comparable conditions.

The culture media at the end of our experiments with (I) and (III) (see p. 1159) contained no radioactive compounds other than the chloride and iodide initially added, showing that in *A. niger* cultures the two dimethylthetins are relatively stable except with respect to the elimination of dimethyl sulphide by S–C fission, observed with the methylmethioninesulphonium iodide (cf. Challenger and Liu, *Rec. Trav. chim.*, 1950, **69**, 334).

The magnitude of the " back-scatter " correction for mercurichlorides (see Part XIV) has now been determined. [*Me*-^{14}C]Dimethyl-β-propiothetin chloride was decomposed with alkali, and the dimethyl sulphide aspirated into 3% aqueous mercuric chloride. The resulting precipitate ($2Me_2S,3HgCl_2$; Blackburn and Challenger, *J.*, 1938, 1878) was filtered on to a standard " plate " and its composition checked by analysis. Its activity per mole was 6—10% higher than that of the original propiothetin chloride. This correction should be applied to all figures for methylation percentages given in Part XIV. Since, however, all conclusions drawn from these figures are relative, this is unnecessary. The existence of such a correction, however, does partly explain why in Table 1 when using D-[*Me*-^{14}C]methionine + L-methionine (Expts. 5 and 6) and L-[*Me*-^{14}C]methionine + D-methionine (Expt. 7), the methylation percentages were greater than the theoretical value of 50%.

Experimental

Radioactive Assay.—The material was plated on " Perspex " discs and counted at infinite thickness, as described in Part XIV (*J.*, 1954, 1760).

The methylation percentage was calculated from the expression

$$\text{Methylation (\%)} = \frac{100}{nf} \times \frac{\text{Radioactivity of methylated product per mole}}{\text{Radioactivity of methyl source per mole}}$$

where n is the number of methyl groups produced by methylation per molecule of the product, and f is the fraction of the total of labelled methyl groups or carbon atoms per molecule which are theoretically labile. Thus, $f = 1$ for the methylmethioninesulphonium ion since both methyl groups are theoretically labile, methionine being formed by the loss of one methyl group. In

the case of the thetins however, *f* was taken as 0·5, since by the loss of one methyl group from the acetothetin methylthioacetic acid is formed which has no labile methyl group (Maw and Du Vigneaud, *J. Biol. Chem.*, **1948**, **176**, 103; Dubnoff and Borsook, *ibid.*, p. 789).

Culture Technique.—The moulds, culture media, and experimental procedure are described in Part XIV.

Preparation of Starting Materials.—The preparation of the radioactive D- and L-methionine was described in Part XIV. DL-[*Me*-^{14}C]methylmethioninesulphonium iodide was prepared from DL-[*Me*-^{14}C]methionine and non-radioactive methyl iodide by Toennies and Kolb's method (*J. Amer. Chem. Soc.*, **1945**, **67**, 849). A paper chromatogram, in butanol–acetic acid, developed with ninhydrin demonstrated the absence of other amino-acids.

Dimethylacetothetin and dimethyl-β-propiothetin chlorides, labelled in one methyl group with ^{14}C, were prepared from radioactive methyl iodide and unlabelled methylthioacetic acid and β-methylthiopropionic acid (Ferger and Du Vigneaud, *J. Biol. Chem.*, **1950**, **185**, 54).

Stable substrates were sterilised under pressure but the two thetins and methylmethioninesulphonium iodide were sterilised by Seitz filtration. The specific rotations of D- and L-methionine were unchanged after sterilisation at 120° for 20—30 min.

Activities (μc per mmole) of Starting Material.—DL-[*Me*-^{14}C]Methionine, 0·356; [*Me*-^{14}C]-betaine hydrochloride, 0·102; D-, 0·725, and L-[*Me*-^{14}C]methionine, 1·440 (for the preparation of these specimens see Part XIV); DL-[*Me*-^{14}C]methylmethioninesulphonium iodide, 0·202; [*Me*-^{14}C]dimethylacetothetin chloride, 0·494; [*Me*-^{14}C]dimethyl-β-propiothetin chloride, 0·601.

These activities were found by comparison with a plated sample of choline picrate (see Part XIV).

The hygroscopic thetin chlorides were kept over phosphoric oxide before counting, which was performed rapidly. Exposure to air for 2—3 min. did not appreciably affect the results.

Determination of Probable "Back-scatter" Correction for Mercurichlorides.—Radioactive dimethyl sulphide mercurichloride was prepared by boiling [*Me*-^{14}C]dimethyl-β-propiothetin chloride with sodium hydroxide and aspirating the sulphide (Challenger and Simpson, *J.*, **1948**, **1591**) into aqueous 3% mercuric chloride. Specimens of the thetin chloride and the sulphide mercurichloride were plated and left for one night over phosphoric oxide and counted with an accuracy of ±2%.

The observed activity for the mercurichloride was 8% higher than that calculated from the activity of the thetin chloride (see above) and the known composition of dimethylsulphide mercurichloride. Hence, the back-scatter correction for a mercurichloride can be roughly estimated as 6—10% (see Part XIV).

The mercurichloride had m. p. 154—155° (decomp.; uncorr.), the usual value obtained by one of us (P. B. D.) for pure specimens. Challenger and Simpson (*J.*, **1948**, **1593**) record m. p. 156—158°. A weighed amount was decomposed with hot alkali, the radioactive dimethyl sulphide recovered, the alkaline suspension of mercuric oxide acidified and treated with hydrogen sulphide, and the mercuric sulphide weighed (Found: Hg, 63·8. Calc. for $C_4H_{12}S_2Cl_6Hg_3$: Hg, 64·1%).

Results.—(*a*) Table 1 shows experiments with *Aspergillus niger* grown on medium G of

TABLE 1.

Expt. no.	Methionine used and its concn. (mmole per flask)	(1) Aspiration time (days)	(2) Methylation (%)	(3) CO_2 (mmole)	(4) Activity (%) recovered as CO_2	(5) Activity (%) recovered from medium in "acid and neutral" fractions
1	DL-[*Me*-^{14}C], 2·0	10	95·2			
		26	86·6	1420	16	
		41	13·3			35
		50	3·2	170	13·9	
2	L-[*Me*-^{14}C], 2·0	19	95	490	3·5	30
		31	99			
3	D-[*Me*-^{14}C], 2·0	18	88	560	4·2	40
		30	100			
4	D-[*Me*-^{14}C], 2·0	11	74	1010	6·5	
		24	93			15
		35	15	770	27·5	
		50	3			
5	D-[*Me*-^{14}C], 1·0 + L-, 1·0	10	61·0	1280	7·0	30
		22	48·0			
6	D-[*Me*-^{14}C], 1·0 + L-, 1·0	13	53·0	Not measured	—	40
7	L-[*Me*-^{14}C], 1·0 + D-, 1·0	10	63·0	1200	9·4	35
		22	37·0			

Part XIV, with sodium selenate (2·5 mmole per flask) as substrate. Dimethyl selenide evolved was collected, and counted, as the mercurichloride, m. p. and mixed m. p. 152—153° (decomp.) in all cases.

In experiments (2) and (3) the cultures developed and spored much better than the others. The yield of dimethyl selenide during the aspiration was only 2·5% compared with the usual 10%, and evolution of selenide ceased completely after 30 days although the food sources of the medium were not exhausted (as shown by the relatively small evolution of carbon dioxide).

Cultures 5 and 7 were made up, grown, and aspirated simultaneously under identical conditions.

Investigation of culture media after aspiration. The cultures were killed by addition of 5—10 c.c. of chloroform, and the mycelium was filtered off, pressed, well washed with water, again pressed, and dried overnight at 30°, and for 2 hr. at 80°. The dry solid was weighed, powdered, plated, and counted.

The radioactivity in the medium was found by counting the viscid solid obtained by evaporating 10% of the medium and washings at 50°/30 mm.

In experiment 1, 40% of the activity originally added as DL-[*Me*-^{14}C]methionine was found in the medium and 10% in the mycelium, the remainder in the carbon dioxide (30%) and dimethyl selenide (20%).

The radioactive material in the medium was probably not methionine since the amount of methylation at the end of the experiment was only 5%. After removal of chloroform at 50—60° the medium was passed slowly through sulphonated cross-linked polystyrene resin to remove bases. These were eluted with 0·2N-ammonia and concentrated by evaporation *in vacuo* over potassium hydroxide.

Only 5% of the original radioactivity was found in the basic fractions, from which methionine was absent (Sullivan test; *J. Biol. Chem.*, 1941, **141**, 871; 1943, **151**, 635; Borsook and Dubnoff, *ibid.*, 1948, **176**, 789).

A chromatogram of the concentrated bases was run on Whatman No. 1 filter paper in butanol–acetic acid. With ninhydrin several spots appeared corresponding to various amino-acids, but not to methionine. No localisation of the radioactivity in any particular spot could be detected.

The effluent from the column, containing acidic and neutral substances, was evaporated. The radioactivity was 35% of the original. Acidic and neutral substances were separated by "Deacidite FF" resin. The "neutral" eluate was almost inactive. The acids (AX) were eluted with 2N-hydrochloric acid and the radioactivity found in the fraction emerging just before the chloride ions. A chromatogram of this fraction, on Whatman No. 54 paper with ethanol–ammonia, was developed with alkaline thymol-blue in ethanol. Four prominent spots at R_F approx. 0, 0·2, 0·45, and 0·6 were obtained but only the third was radioactive. The acid was separated by running a large paper "strip" falling-front chromatogram with a portion of the concentrated fractions. The radioactive band at R_F 0·5 was washed out with water, and the solution evaporated in a vacuum over potassium hydroxide, giving 20 mg. of a viscous brown material of high activity. Several rising-front chromatograms run with this material in ethanol–ammonia showed a radioactive acid spot at R_F 0·45 and a fainter inactive spot at R_F 0·2. The aqueous extract of the main acid spot contained nitrate but no sulphate, sulphite, or chloride. Fusion of the viscous radioactive acid with sodium gave a strong odour of an unidentified sulphur compound. The nitroprusside test was strongly positive; the nitrogen test very faintly positive [(?) nitrate]; halogen was absent. The acids (AX) gave an inactive 2 : 4-dinitrophenylhydrazone but the active material gave no such derivative. The unknown compound is therefore not a keto-acid but contains sulphur and, possibly, nitrogen, and is probably a derivative of the original methionine with radioactive carbon still attached to sulphur. That so much of the original radioactivity is present in a single compound supports this view.

The Sullivan test however was negative, showing that methylthio-acids such as 2-methylthiopropionic or methylthioacetic acid were absent, and the R_F's of these acids when run simultaneously in ethanol–ammonia were 0·75 and 0·65 respectively, compared with 0·45 for the unknown acid. Oxidation of methylthioacetic acid to the sulphone lowered the R_F only to 0·55.

Experiment 4 continued much longer than the others. The bases, after separation as before, contained no methionine and were only slightly radioactive. The small amount of the "acid and neutral" fraction indicated almost complete exhaustion of food sources in the medium, and 90% of the sucrose was converted into carbon dioxide. Very little "acid and neutral" radioactive material was obtained. The activity was contained in one acid spot of R_F 0·45 in

alcohol–ammonia and 0·15 in acetone–ammonia. The radioactive acids in experiments 1 and 4 are therefore identical. Much of this acid was probably oxidised as the activity of the carbon dioxide during the last 14 days was very high. In experiments 2—7 the basic fractions containing amino-acids from the younger cultures were highly radioactive. Paper chromatograms in butanol–acetic acid, developed with ninhydrin, showed several spots including a prominent methionine spot which contained all the radioactivity, showing that methionine did not all disappear in four weeks.

TABLE 2.

Expt. no.	Thetin	Concn. (mmole per flask)	Aspiration time (days)	Methylation (%)	CO_2 (mmole)	Activity (%) recovered as CO_2
8	(I) $Cl^-\{^{14}CH_3\cdot S(^{12}CH_3)\cdot CH_2\cdot CO_2H$	2	11	1·4	520	5·2
			22	2·3		
9	„ „	2	14	1·4	360	2·0
10	(II) $Cl^-\{^{14}CH_3\cdot S(^{12}CH_3)\cdot CH_2\cdot CH_2\cdot CO_2H$	2	11	1·8	500	4·4
			22	2·8		
11	(III) $I^-\{^{14}CH_3\cdot S(^{12}CH_3)\cdot CH_2\cdot CH_2\cdot CH(NH_2)\cdot CO_2H$	2	6	35·5	610	2·4
			11	36·5		
			14	28·7		
—	$Cl^-\{^{14}CH_3\cdot N(^{12}CH_3)_2\cdot CO_2H$	2	11	11·1	948	22·1
			22	19·6		
			40	22·6		

(*b*) Table 2 shows experiments with thetins and *A. niger* 17 grown on medium G (300 c.c. per flask) with sodium selenate (2·5 mmole per flask) as substrate. Dimethyl selenide was collected and counted as mercurichloride (mixed m. p. 152—153°).

Experiments 10 and 11 each yielded approx. 1% of radioactive dimethyl sulphide. This was separated from dimethyl selenide as described in Part XIV. The yield of selenide in experiments 8—10 was approx. 8% in 22 days and in experiment 11 approx. 12% in 14 days.

In experiment 8, where labelled dimethylacetothetin chloride was used a balance was worked out in the same way as in experiment 1; the results were: basic fractions of medium 75%, neutral and acidic fractions 0, carbon dioxide 5%, dimethyl selenide 0·5%, and mycelium 15% (total 95·5%).

Two chromatograms in butanol–acetic acid on Whatman No. 54 paper developed with ninhydrin and bromophenol-blue, respectively, revealed a basic strongly radioactive spot, giving no colour with ninhydrin and identical in R_F with the dimethylacetothetin spot; so much thetin was unchanged. Challenger and Liu (*Rec. Trav. chim.*, 1950, **69**, 338) found that dimethylacetothetin bromide yields no dimethyl sulphide with *S. brevicaulis*. The absence of radioactivity in the acid fraction is important and shows that no methylthioacetic acid had accumulated. This could arise by demethylation of the thetin and would have been easily detected as the thetin salt was strongly radioactive. Possibly both methyl groups are oxidised. [The behaviour of methylthioacetic acid with *A. niger* is unknown but in bread cultures of *S. brevicaulis* methyl- and ethyl-thioacetic acids give neither alkanethiol nor alkyl methyl sulphide (Lowther, Thesis, Leeds, 1949; Challenger and Charlton, *J.*, 1947, 425).]

The "acid and neutral" fractions of the medium from experiment 11 which had originally contained DL-[*Me*-^{14}C]methylmethioninesulphonium iodide were non-radioactive, and methionine was not detected in the basic fractions, the radioactivity being located in one spot on a paper chromatogram run in butanol–acetic acid and developed with ninhydrin or bromophenol-blue. This corresponded exactly in R_F and colour to that given by the methylmethioninesulphonium ion. This fraction gave with phosphotungstic acid a radioactive precipitate and an almost non-radioactive filtrate. Apparently the methylmethioninesulphonium ion is not degraded in the same way as methionine since neither the amino-acid itself nor the acid of R_F 0·45 was found in the medium.

(*c*) Table 3 shows results with *S. brevicaulis* grown on bread with sodium selenate (2·5 mmole per flask). Dimethyl selenide was collected and counted as mercurichloride. Aspiration was through mercuric cyanide and (*a*) acid and (*b*) neutral mercuric chloride. The thetins were labelled in one methyl group.

The experiments were simultaneous and m. p.s and mixed m. p.s for the purified mercurichloride were 152—153°. Results are based on radioactivities of precipitates collected in acid mercuric chloride only. These, even when crude, were almost inactive and

free from sulphides (by m. p.). The slight radioactivity present was unchanged on the usual purification (Part XIV). The crude precipitates from experiments 12 and 13 (from material collected in *neutral* mercuric chloride) were highly radioactive. This activity was removed on purification and was due to dimethyl sulphide mercurichloride formed by S–C fission of the

TABLE 3.

Expt. no.	Thetin	Concn. (mmole per flask)	Aspiration time (days)	Methylation (%)	CO_2 (mmole)	Activity (%) recovered as CO_2
12	(I)	2·0	7	0·9	1830	9
			14	1·6		
13	(II)	2·0	7	0·8	2050	8
			14	1·5		
14	$Cl^-[^{14}CH_2{\cdot}NMe_2{\cdot}CH_2{\cdot}CO_2H$	2·0	7	4·1	1510	19
			14	2·0		

thetins. This fission was only 0·5% in experiment 12 and 2·0% in experiment 13. The activity of the neutral mercuric chloride precipitate from experiment 14, however, was of the order of that of the acid mercuric chloride precipitate and was unchanged by purification.

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Gum Ghatti (Indian Gum). The Composition of the Gum and the Structure of Two Aldobiouronic Acids derived from it.

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Gum ghatti on hydrolysis yields a mixture of L-arabinose (5 mols.), D-galactose (3 mols.), D-mannose (1 mol.), xylose (½ mol.), D-glucuronic acid (1 mol.), and traces (below 1%) of methylpentose. On graded hydrolysis the gum gives two aldobiouronic acids, namely 6-*O*-β-D-glucuronosyl-D-galactose and 2-*O*-β-D-glucuronosyl-D-mannose. Oxidation of the gum with periodate has been studied.

THE chemistry of gum ghatti (Indian gum) from *Anogeissus latifolia*, Wall (family, Combretaceæ), was investigated by Hanna and Shaw (*Proc. S. Dakota Acad. Sci.*, 1941, **21**, 78) who reported the presence of pentosan (50%) and galactose or galacturonic acid (12%) in the gum. They isolated L-arabinose after partial hydrolysis with acid and obtained a resistant aldobiouronic acid of equivlaent weight 352. In the present work a beginning has been made in the study of the detailed molecular structure of this important gum.

A purified sample of the gum had an equivalent weight of about 1600 (by titration with alkali) and on complete hydrolysis yielded L-arabinose, D-galactose, D-mannose, and D-glucuronic acid. Some xylose and a trace of methylpentose were also present but it is not certain whether these residues are present in the molecular structure.

The uronic anhydride content, determined by the carbon dioxide liberated by 19% hydrochloric acid at 145° (McCready, Swenson, and Maclay, *Ind. Eng. Chem. Anal.*, 1946, **18**, 290), was 12·0% (calculated for a substance of equivalent weight 1600, 11·0%). The pentosan content of the gum acid was 46·4%, calculated as anhydroarabinose from the liberated furfuraldehyde determined as thiobarbiturate (Marshall and Norris, *Biochem. J.*, 1937, **31**, 1293), account being taken of the furfuraldehyde yielded by the uronic acid residues (Norris and Resch, *Biochem. J.*, 1935, **29**, 1590).

After complete hydrolysis of the gum, determinations of the sugars separated on paper

chromatograms were carried out by the periodate method (Hirst and Jones, *J.*, 1949, 1659). The following results were obtained: arabinose 41·1%, xylose 2·7%, galactose 26·7%, mannose 8·3%, the figures in each case being calculated for the anhydro-sugar residue.

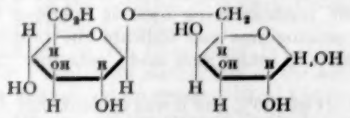
A gum acid with equivalent weight 1600 consisting of 5 arabinose residues, 3 galactose residues, 1 mannose residue, and 0·5 xylose residue per unit of uronic anhydride, would contain the following percentages of anhydro-sugars: arabinose 41·2% (found, 41·1%), galactose 30·4% (found, 26·7%), mannose 10·1% (found, 8·3%), xylose 4·1% (found, 2·7%), uronic anhydride 11·0% (found, 12·0%).

When the gum acid was boiled in aqueous solution 4 moles of L-arabinose per equivalent were readily removed, probably because they are present in the furanose form and located in the outer parts of the molecule. The remaining arabinose residue was less easily removed by autohydrolysis, leaving a resistant degraded gum containing some 4% of arabinose residues possessing an equivalent weight of about 1000.

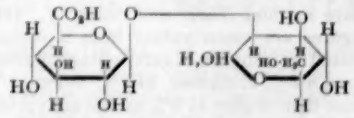
On reaction with periodate, 80% of the arabinose residues in the gum acid are oxidised; on the other hand, only about one third of the galactose residues are attacked. During the reaction *ca.* 3 moles of formic acid are produced per equivalent. These results are understandable if 80% of the arabinose residues in the gum molecule possess adjacent hydroxyl groups and are present as L-arabofuranose residues linked through $C_{(1)}$ and $C_{(5)}$. It is probable that the L-arabinosyl linkages are α in type, since on partial hydrolysis, the specific rotation changes from $[\alpha]_D$ −48° for the gum acid to +6° for the degraded gum. It also follows that most of the galactose residues are engaged in linkages such as $C_{(1)}$–$C_{(3)}$ which exclude the presence of contiguous hydroxyl groups. In this connection it will be recalled that D-galactopyranose residues linked through $C_{(1)}$ and $C_{(3)}$ have been encountered in most of the plant gums previously examined. In view of the amount of formic produced during the oxidation with periodate it is likely that the D-galactose residue which is attacked is linked through positions $C_{(1)}$ and $C_{(6)}$.

After partial hydrolysis of the gum acid with aqueous sulphuric acid a product containing two aldobiouronic acids was obtained. One of these contained D-mannose and a uronic acid whilst the other liberated D-galactose on further hydrolysis. Proof of their structure was obtained by methylation of the mixture of aldobiouronic acids and subsequent examination of the methylated sugars liberated on hydrolysis. The uronic acid fraction was then identified as 2 : 3 : 4-tri-*O*-methyl-D-glucuronic acid after conversion into the crystalline methyl ester of 2 : 3 : 4-tri-*O*-methyl-D-saccharolactone. The neutral fractions were 3 : 4 : 6-tri-*O*-methyl-D-mannose and 2 : 3 : 4-tri-*O*-methyl-D-galactose, identified by their rates of movement on chromatograms and by their properties after isolation in the crystalline state.

The portion of the gum molecule most resistant to hydrolysis consists therefore of two aldobiouronic residues, namely 6-*O*-β-D-glucuronosyl-D-galactose (I) and 2-*O*-β-D-glucuronosyl-D-mannose (II), which appear to be present in approximately equal proportions, since the ratio galactose : mannose was 1 : 1 in the mixture of aldobiouronic acids obtained after partial hydrolysis of the gum with 0·16N-acid. The specific rotation of the methylated aldobiouronic acids indicates that the glucuronosyl junction is β in type.



(I)



(II)

In respect of the constituent sugars, gum ghatti resembles damson gum (Hirst and Jones, *J.*, 1938, 1174) and cherry gum (Jones, *J.*, 1939, 558), both of which are built up of residues of D-glucuronic acid, L-arabinose, D-xylose, D-galactose, and D-mannose. All three gums yield on partial hydrolysis the same aldobiouronic acid, 2-*O*-β-D-glucuronosyl-D-mannose (II). Gum ghatti and cherry gum show further similarity in the large proportion of L-arabinose residues present in their molecular structures, but much more work with both gums will be necessary before a detailed structural comparison will be possible.

It is of interest in this connection that gum ghatti gives also on partial hydrolysis another aldobiouronic acid, namely 6-*O*-β-D-glucuronosyl-D-galactose (I) which is a characteristic feature of gum arabic and other gums of the *Acacia* group.

Experimental

Purification of the Gum.—The commercial sample of gum ghatti (obtained from Messrs. Eimer and Amend, New York) consisted of yellowish nodules, soluble in water with the exception of a few fragments of bark, etc. The aqueous solution gave a positive test for calcium. The gum acid was precipitated by pouring a filtered aqueous solution of the gum into ethanol, acidified with hydrochloric acid to about 0·1N. The precipitate was purified by the method described for damson gum (Hirst and Jones, *J.*, 1938, 1174) and was dried at 40—50° under reduced pressure.

It was noticed that during the precipitation a small portion of the gum acid (*ca.* 2%) separated as a finely dispersed suspension. This was separated, after addition of ether to the mixture, and showed the same analytical properties (equivalent weight, optical rotation, pentosan content) as the main batch, and on complete hydrolysis it liberated the same sugars. It appeared therefore to be identical with the main portion.

Analysis of the Purified Gum Acid.—The figures given below are mean values from a series of analyses carried out with two separately prepared batches; no significant difference in properties was observed between the two preparations: $[\alpha]_D^{20}$ −50° (approx.) (as Na salt; *c*, 1·0 in H_2O); equivalent weight by acid acidimetry, 1600; carbon dioxide liberated when heated with 19% hydrochloric acid, 2·99% (corresponding to 12·0% uronic anhydride) (calc. for a polysaccharide of equiv. wt. 1600: CO_2, 2·75%, uronic anhydride, 11·0%); pentosan content, 46·4% (as anhydroarabinose; calc. from the amount of furfuraldehyde evolved under standard conditions); ash (as sulphate), <0·5%; N_2 (Kjeldahl), <0·4%; acetyl groups, <0·4%. The gum acid had an apparent methoxyl content (Zeisel estimation), 2·2%; but this was probably due to esterification during the precipitation by acid ethanol. The crude gum had a negligible OMe content (<0·1%). A small iodine number observed with the purified gum acid (5·6 ml. of 0·1N-iodine per 1·0 g.) may also be due to ethyl alcohol introduced during the purification. The gum acid did not reduce Fehling's solution.

Examination by Paper Chromatography of the Sugars produced on Complete Hydrolysis of the Gum Acid.—A solution (0·5%) of gum acid in 2N-sulphuric acid was heated for 24 hr. in a sealed tube immersed in a boiling-water bath. The solution was neutralised (Amberlite IR-4B) and then concentrated under reduced pressure. On chromatograms including reference substances and run with several solvent systems, the four sugars, galactose, mannose, arabinose, and xylose, were detected. Spots corresponding to more resistant parts of the gum (*e.g.*, oligosaccharides) were not observed. Another solution, obtained as described above, was neutralised by barium carbonate, followed by removal of the barium neutral filtrate by Amberlite IR-120. The solution was then concentrated under reduced pressure and examined on paper chromatograms obtained under the conditions described for the detection of uronic acids (Partridge, *Biochem. J.*, 1948, 42, 238). Spots corresponding to glucuronic acid and glucurone were observed.

Quantitative Determination of the Sugars present in the completely Hydrolysed Solution.—After paper-chromatographic separation of the sugars, their quantities were determined by the periodate method (Hirst and Jones, *J.*, 1949, 1659), D-ribose being used as reference sugar. The figures are mean values from a series of chromatograms and indicate the proportions (calculated as anhydro-sugars) obtained from 100 parts of intact gum acid; galactose, 26·7%, mannose, 8·3%, arabinose, 34·0%, xylose, 2·7%.

These figures plus 11·0% uronic anhydride fall short of 100% and it was evident that decomposition had taken place during the hydrolysis. This is mostly due to loss of pentose since the figure for anhydroarabinose by the furfuraldehyde method was 46·4%. Subsequent experiments showed that most of the pentose is liberated during 60 min. in the sealed-tube experiments. It follows that the free arabinose was submitted to more than 20 hours of heating in a boiling-water bath in an acid medium. As shown in the following section it is, however, possible by using milder conditions of hydrolysis to obtain quantitative results for arabinose which are in good agreement with the furfuraldehyde determination.

Quantitative Determination of Arabinose after Autohydrolysis of the Gum Acid and after Hydrolysis of the Gum with 1·0N-Formic Acid.—A 2% aqueous solution of gum acid was heated

in a boiling-water bath until the optical rotation became constant at $[\alpha]_D^{20}$ +49° after 44 hr. Paper chromatography showed that, in addition to the liberated arabinose and traces of xylose, galactose began to split off after 44 hr. Determination of the arabinose on the chromatograms showed that an amount corresponding to 34·4% of anhydroarabinose, or 4 residues per equivalent weight (1600), was liberated.

Hydrolysis of the gum acid with N-formic acid in a boiling-water bath for 20 hr. proceeded with little apparent decomposition. The hydrolysis products were separated chromatographically. As in the case of the autohydrolysis, xylose and galactose were liberated in amounts too small for accurate determinations. (*A*) Gum acid (544·6 mg.) and D-ribose (199·5 mg.) were dissolved in N-formic acid (10 ml.) and refluxed in a boiling-water bath for 20 hr. Arabinose liberated: 42·7% (calc. as anhydroarabinose). This amount did not increase during continued heating in 3N-formic acid. (*B*) D-Ribose (175·8 mg.) was added after the hydrolysis (20 hr.) of gum acid (573·0 mg.) in N-formic acid (10 ml.). Arabinose liberated: 39·5% (calc. as anhydroarabinose). It is likely that method (*A*) will give results slightly above the correct figure, whereas method (*B*) probably involves a slight error in the opposite direction. The mean value (41·1%; corresponding to 5 residues of arabinose per equiv.) is in reasonable agreement with the results of the furfuraldehyde determination (46·4%) when account is taken of the presence of xylose (*ca.* 3%) and rhamnose (*ca.* 1%) residues.

Examination of the Degraded Gum.—An aqueous solution of the gum acid was heated for 48 hr. in a boiling-water bath ($[\alpha]_D^{20}$ +49°). It was then filtered and concentrated to a thin syrup at 40—50° under reduced pressure. The syrup was poured into ethanol, and the precipitated polysaccharide washed repeatedly with hot methanol and dried at 40° under reduced pressure (yield 25%). It had $[\alpha]_D^{20}$ +6° (as sodium salt; *c*, 1·0 in H_2O); equiv. (by acidimetry), 985; equiv. (by determination of uronic anhydride), 977. Pentosan, calculated as anhydroarabinose, 3·7%, from furfuraldehyde determinations.

Determinations were made after paper-chromatographic separation of the sugars liberated on complete hydrolysis of the degraded gum (by heating it with 2N-sulphuric acid for 24 hr. in a sealed tube immersed in a boiling-water bath). The following mean values were obtained (calc. as percentage of anhydro-sugar in the intact degraded gum): galactose, 48·5%; mannose, 11%; arabinose, 3·5%; xylose, 1%. Account being taken of the presence of 17·2% of uronic anhydride, the total is less than 100%, owing probably to decomposition during hydrolysis. Approximately one sugar residue per equivalent is missing.

Isolation of L-*Arabinose and* D-*Galactose, by Stepwise Hydrolysis of the Gum Acid.*—L-*Arabinose.* After autohydrolysis and precipitation of the degraded gum acid, the mother liquor was concentrated under reduced pressure to a thick syrup, which was repeatedly extracted with boiling ethanol. The combined alcoholic extracts on concentration yielded crystalline L-arabinose (yield 10%), still contaminated with traces of xylose, but after recrystallisation from ethanol the substance was chromatographically homogeneous and then had m. p. and mixed m. p. 156—158°, $[\alpha]_D^{20}$ +103° (*c*, 1·0 in H_2O).

D-*Galactose.* Degraded gum acid was partly hydrolysed with sulphuric acid (2N) in a boiling-water bath. After 4 hr. the solution was neutralised with barium carbonate, filtered, concentrated (reduced pressure), and poured into ethanol. The barium salts were filtered off and the mother liquid was concentrated (reduced pressure) to dryness. On trituration of the residue with hot methanol crystalline D-galactose separated (yield 2%); chromatographically pure it had m. p. and mixed m. p. 162—165°. Further evidence that this was the D-isomer was provided by the isolation of *O*-methyl-D-galactoses on hydrolysis of the methylated degraded gum (unpublished results).

Oxidation of the Gum Acid by Periodate.—Portions (10 ml.) of an aqueous solution (0·0025N; neutral to methyl red) of the sodium salt of the gum acid were allowed to react with sodium metaperiodate (0·05M; 10 ml.) at room temperature in the dark. The periodate uptake was determined by the arsenite method, and the formic acid by titration with aqueous sodium hydroxide (methyl red as indicator) after addition of ethylene glycol. The following results were obtained as mean values of two series of analysis:

Time (hr.)	2	4	8	20	48	60	96
Periodate reduced (moles)	7·0	8·4	9·1	9·9	10·5	10·7	10·8
Univalent acid liberated (moles)/equiv. of gum acid	2·5	2·8	3·0	3·1	3·3	3·4	3·4

Examination of the Material remaining after Oxidation of the Gum with Periodate.—Preliminary qualitative determinations showed that some galactose, mannose, and arabinose still remained intact in the oxidised gum. But neither uronic acid nor xylose could be detected.

Gum acid (270 mg.) was oxidised with sodium metaperiodate (700 mg.) for 48 hr. The oxidation was stopped by the addition of ethylene glycol, and the solution was then dialysed against running water until inorganic ions had been removed (5 days). The solution was concentrated (reduced pressure) to about 30 ml., made acid (2N) with sulphuric acid, and heated for 20 hr. at 98°. It was neutralised with barium carbonate, and the concentrated filtrate was examined on paper chromatograms. Analyses showed that the following sugars were present: arabinose, 9·2%; galactose, 20·8%; mannose, 7·1% (the figures give the amount of each sugar remaining unoxidised expressed as percentages of the weight of the original gum acid).

Examination of the Product obtained by Graded Hydrolysis of the Gum.—Hydrolysis of the gum with aqueous sulphuric acid could not be followed beyond the early stages polarimetrically or by determination of the iodine number, since even with 0·16N-acid considerable destruction took place (brown colour and precipitate). After 24 hr. at 100°, the solution was neutralised and the acidic materials were isolated as the barium salts [Yields: (*a*) Product *A* from hydrolysis with 0·16N-acid; 15% with Ba content, 18·6%. (*b*) Product *B* from hydrolysis with 0·5N-acid; 8% with Ba content, 23·0%. (*c*) Product *C* from 0·9N-acid; 1·5%]. All three products liberated glucuronic acid, galactose, and mannose on further hydrolysis. Quantitative paper-chromatography showed that galactose and mannose were liberated in equimolecular proportions from product *A* and in the ratio 1 : 1·5 from product *B*. The barium content is too high to account for the presence of a trisaccharide (aldotriouronate) or a mixture of an aldobiouronic acid and a resistant oligosaccharide (barium calc. for aldobiouronate, 16·2%; for aldotriouronate, 11·7%).

Barium ions were removed from an aqueous solution, with Amberlite IR-120, and the resulting solution was examined on paper-chromatograms run with the solvent systems (I) (amyl alcohol–pyridine–water; 7 : 7 : 6), and (II) (ethyl acetate–formic acid–acetic acid–water; 18 : 1 : 3 : 4) (both systems, "one-phase"). Two spots showing reducing and acid properties (bromophenol blue) were observed, moving at rates characteristic of disaccharides; in solvent (I) $R_{galactose}$, 0·45 and 0·55 (galactose, 1·00); in solvent (II) $R_{glucurone}$, 0·14 and 0·23 (glucurone 1·00). Glucuronic acid which is present in traces was clearly separated from the other spots in system (II).

Chromatograms with larger quantities of product *A* were run [solvent (I)] on thick paper (Whatman 3MM). The two spots were eluted and on hydrolysis of the eluates the upper spot yielded glucoronic acid and galactose whereas the lower spot yielded glucuronic acid and mannose (paper-chromatography). Final proof of the presence of two distinct aldobiouronic acids in the mixture emerged from the methylation studies described below.

Large-scale Preparation of the Barium Aldobiouronates.—Gum acid (100 g.) was dissolved in 0·45N-sulphuric acid (2 l.) and heated in a boiling-water bath for 24 hr. The filtered solution was neutralised with barium carbonate (150 g.) at 80° with stirring, and the liquid portion was decanted, centrifuged, and concentrated at 40—50° (reduced pressure) to a syrup which was poured into alcohol. The precipitated barium salts were washed with hot alcohol (crude yield, 25 g.), purified by 3 successive precipitations and washed with alcohol (yield, 10 g.) [Found: OMe, negligible; adsorbed free sugars (by paper-chromatography)—traces of galactose and arabinose, and traces of glucuronic acid (all below 1%); Ba, 23·0% (calc. for barium aldobiouronate, 16·2%); uronic anhydride, 44·0% (calc. for barium aldobiouronate, 41·5%); galactose (as anhydro-sugar), 15·8%; mannose (as anhydro-sugar), 23·7%; (both determined by paper-chromatography after hydrolysis)]. The total hexose anhydride is therefore 39·5% (calc. for a barium aldobiouronate, 38·2%).

Isolation of a Methylpentose as Hydrolysis Product.—The alcoholic washings from the large-scale preparation of the barium salts of aldobiouronic acids (see previous section) were concentrated to dryness under reduced pressure. The product gave on chromatographic examination, in addition to the spots expected, a weak spot which moved at the rate of rhamnose. Determination by Nicolet and Shinn's method (*J. Amer. Chem. Soc.*, 1941, **63**, 1456) showed the presence of methylpentose in amount corresponding to about 1% of the gum.

Methylation of the Aldobiouronic Acids.—The barium salts (9 g.) were dissolved in water (100 ml.) and methylated three times with dimethyl sulphate and sodium hydroxide in an atmosphere of nitrogen with vigorous stirring. (1) Dimethyl sulphate (100 ml.) was added and then sodium hydroxide (200 ml.; 30%) dropwise at a temperature below 30°. (2) Solid sodium hydroxide (50 g.) was dissolved in the mixture the following day and dimethyl sulphate (100 ml.) was added dropwise at a temperature below 35—40°. The mixture was heated for 30 min. on a boiling-water bath, cooled, partly neutralised (H_2SO_4), and filtered. (3) The concentrated (at reduced pressure) filtrate was again methylated by dimethyl sulphate (50 ml.)

and sodium hydroxide (100 ml.; 30%) at below 40°. The mixture was finally heated to 80° for 30 min., cooled, acidified with sulphuric acid, and repeatedly extracted with chloroform. The combined extracts were concentrated to a syrup under reduced pressure, and the residue (5 g.) was further methylated with methyl iodide and silver oxide. The product (a yellow, viscid syrup; 4·7 g.) was distilled, giving the following fractions (temperatures are those of the heating bath): (I) a bright yellow, mobile syrup (0·80 g.), b. p. 185—190°/0·1 mm. (Found: OMe, 49·8%); (II) nearly solid, brownish yellow (1·4 g.), b. p. 200°/0·03 mm. (Found: OMe, 49·9%), $[\alpha]_D^{20}$ −24·2° (*c*, 5 in MeOH); (III) residue, b. p. >230°/0·03 mm. (Found: OMe, 50·1%).

Samples of the fractions were hydrolysed and the methylated sugars liberated were examined on paper-chromatograms. None of the fractions gave tetramethylgalactose or tetramethylmannose. Fraction II gave spots of methylated uronic acid, trimethylgalactose, R_G 0·65, and a trimethylmannose, R_G 0·80. Fraction I gave mainly methylated uronic acid and traces of the two trimethyl sugars. The residue (fraction III) gave the same spots as fraction II, but in addition there were two unidentified sugars (traces only), having R_G 0·50 and 0·78, respectively.

Separation and Identification of the Hydrolysis Products of the Methylated Aldobiouronic Acids (Fraction II).—Fraction II (1·2 g.) was hydrolysed with N-sulphuric acid (25 ml.) for 13 hr. in a boiling-water bath. The solution was neutralised ($BaCO_3$), filtered, and evaporated, leaving a yellowish powder (1·0 g.), which was exhaustively extracted with dry ether. The product was a chromatographically-homogeneous barium salt of methylated glucuronic acid (*Y*) (0·50 g.).

The ethereal extract on evaporation gave a yellowish syrup (*X*) (0·50 g.), which was separated into its constituents on cellulose (working dimensions, 2·5 × 75 cm.), *n*-butanol–light petroleum (b. p. 100—120°) (30/70 by vol.), saturated with water, being used as mobile phase. The eluate was collected in portions (6—7 ml.), and two fractions were obtained: (i) (0·10 g.), 3 : 4 : 6-tri-*O*-methyl-D-mannose, R_G 0·80, m. p. and mixed m. p. 101—102°, $[\alpha]_D^{20}$ +10° (*c*, 2 in H_2O); (ii) (0·05 g.), 2 : 3 : 4-tri-*O*-methyl-D-galactose, R_G 0·64 (Hirst and Jones, *Discuss. Faraday Soc.*, 1949, **7**, 271). Fraction (ii) crystallised as the hydrate when kept. After recrystallisation from ether, it had m. p. 78°, with some sintering at 73° (see Smith, *J.*, 1939, 1734) and showed a large depression of m. p. when mixed with 2 : 4 : 6-tri-*O*-methyl-D-galactose (R_G 0·67).

The barium salt (*Y*) was dissolved in water, and barium ions were removed with Amberlite IR-120. The tri-*O*-methyl-D-glucuronic acid remaining in solution was oxidised with bromine water to 2 : 3 : 4-tri-*O*-methyl-D-saccharic acid (0·25 g.) which was esterified with methanolic hydrogen chloride. The ester was distilled (b. p. 160°/0·3 mm.); the distillate ($[\alpha]_D$ positive) crystallised when nucleated with the methyl ester of 2 : 3 : 4-tri-*O*-methyl-D-saccharolactone, m. p. and mixed m. p. 109—110°. The two aldobiouronic acids obtained by partial hydrolysis of the gum are therefore 2-*O*-β-D-glucuronosyl-D-mannose and 6-*O*-β-D-glucuronosyl-D-galactose.

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Surface Forces of Lecithin Sols in the Presence of Some Inorganic Salts.

By P. H. Elworthy and L. Saunders.

[Reprint Order No. 5922.]

A sensitive apparatus has been devised for the measurement of surface forces at sharp boundaries formed between lecithin sols and water. The ring-pull technique for the measurement of surface force has been used and a new type of cell for making the boundaries is described.

The effects of various inorganic salts on the surface force have been studied. If the lecithin sol was first stripped of all small ions by treatment with exchange resins, only a very small surface force could be measured in the presence of potassium or sodium chloride. The addition of very low concentrations of bivalent metal chlorides caused a considerable increase in the surface force, the order of activity being $CdCl_2 > MgCl_2 > CaCl_2 > BaCl_2$.

The properties of lecithin films at sol–water boundaries are of interest in relation to biological membranes. In a previous paper (*J.*, 1953, 1310) preliminary measurements of small "interfacial tensions" or "surface forces," at sharp boundaries formed between lecithin sols and water, were reported. In this paper, a more sensitive apparatus for their measurement is described, and the results of some experiments on the effect of inorganic salts on these surface forces are recorded.

The surface forces, γ (dynes/cm.), have been calculated by the formula $mg = 2\pi\gamma d$ where m is the force in grams-weight required to pull a circular platinum ring of diameter d cm. through the sol–water boundary.

The extremely small density difference between the sols and water precludes the use of correction factors of the type proposed by Harkins and Jordan (*J. Amer. Chem. Soc.*, 1930, **52**, 1751). Also this surface is more nearly akin to the force of extension of a membrane than to the work of extension of a simple liquid–liquid interface.

Experimental

Apparatus.—The cell in which the boundaries were made (Fig. 1) consists of two parts: the male part of a 25-mm. ground-glass joint, the tubing above which was drawn to a constriction (*A*), 0·3-cm. wide, and 1 cm. above the joint; and the female part of the joint, the tubing below which was closed at the bottom (*B*). Halfway up this lower tube was sealed a side-arm with a fine horizontal jet (*C*) inside the cell; near the bottom on the opposite side, was a filling tube (*D*). Rubber tubing joined the jet side-arm to a stopcock, by which the rate of flow of liquid from the cell could be controlled. The filling tube could be closed by a rubber tube and a clip.

The platinum ring hung inside the cell below the level of the jet (*C*), suspended from the arm of a precision torsion balance, by means of a fine Nylon thread. The cell was immersed in a water-thermostat, controlled to $\pm 0{\cdot}05°$. To prevent errors due to the Nylon suspension's touching the sides of the constriction, the clamp holding the cell was attached to a centering device by which the cell could be moved smoothly in two mutually perpendicular directions until the suspension was exactly in the centre of the constriction.

The balance had a capacity of 5 mg. and a mirror scale which could be read to 0·01 mg. It stood on a platform which was moved up and down a stout metal pillar by means of a rack and pinion. By operating the pinion, the balance, and therefore the platinum ring, could be raised or lowered slowly and smoothly.

The platinum ring was rendered completely planar and circular by careful tapping in a groove cut in a brass plate. To ensure that it was horizontal when suspended, it was hung over a mirror (Harkins and Jordan, *loc. cit.*). Its mean diameter (1·027 cm.) was measured by means of a Cambridge Universal Measuring Machine.

Materials.—Lecithin was prepared from a cold, ethanol extract of egg powder by formation and purification of the cadmium chloride complex (Pangborn, *J. Biol. Chem.*, 1949, **188**, 471).

The cadmium chloride was removed by adding methanolic ammonia to a solution of the purified complex in ammonia, and the lecithin was recrystallised twice from 4 : 1 acetone–ethyl methyl ketone. After being washed with acetone and dried in a vacuum, it was a crisp, cream-coloured solid which appeared uniformly crystalline under the polarising microscope, exhibiting parallel extinction. It was dissolved in dry ethanol and passed through a column of mixed weak anion- and cation-exchange resins to remove traces of cadmium- and amino-containing impurities. The lecithin gave, on analysis, N 1·9%, P 4·1%, I no. 66·7, $[\alpha]_D^{20}$ 7·54° (10% solution in EtOH). Lecithin of the mean fatty acid composition found by Riemenschneider, Ellis, and Titus (*ibid.*, **1938**, **126**, 255) requires N 1·8%, P 4·0%, I no. 74.

Water was prepared by distillation in a seasoned all-glass still.

Inorganic salts were " AnalaR " materials.

Preparation of Sols.—The lecithin sols were made by evaporating to dryness a portion of alcoholic solution of lecithin of known concentration. The dry lecithin was then shaken with water until completely dispersed. The sol was freed from included air by means of a filter-pump and was passed through a column of mixed ion-exchange resins; here any small ions still present were completely removed, the specific electrical resistance at 20° of a 0·5% sol rising from 0·11 to 0·75 megohm cm., while the loss in weight of solids was less then 2%. The resulting sol had pH 7. By this method complete removal of the particularly persistent cadmium ion (Macpherson, *Nature*, **1954**, **173**, 1195) was ensured. The salt under investigation was added to the sol after ion-exchange, and the whole then made up to the required volume. About 25 ml. of sol were required for each measurement.

Boundary Formation.—Both the sol and the water or solution with which the boundary was to be formed were preheated to 35° to prevent formation of bubbles on the walls of the cell which might rise into the constriction and prevent free movement of the suspension. The sol was poured into the lower part of the cell with the jet (*C*) filled with water. The Nylon suspension, with ring attached, was passed through the constriction in the upper part of the cell, and the joint was fitted together so that the ring hung in the cell. Sol was then drawn in through the constriction by alternately applying and releasing pressure on the filling tube (*D*) until the cell was filled to a level above the constriction. The cell was placed in the thermostat and allowed to reach temperature equilibrium; liquid was then run out of the jet (*C*) until the sol level reached a point halfway up the constriction. The upper liquid was introduced carefully so as to fill the top part of the cell, the constriction preventing mixing of the two liquids and enabling an initial sharp boundary to be formed between them. The tap on the jet (*C*) was then opened to permit sol to flow out of the cell, causing the boundary to move downwards; despite its increased area the boundary remained sharp, providing the interior walls of the cell were treated with a " methyl silicone " (" Repelcoat "). When the boundary reached the level of the jet (*C*), flow-off was continued to give a final sharpening.

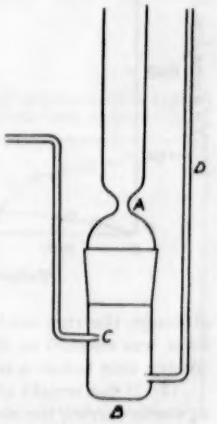


FIG. 1. *Cell for surface-force measurements.*

There is very little density difference between a lecithin sol and water and, although boundaries could be formed directly, there were many failures. To facilitate boundary formation a relatively inert weighting agent was added to the sols, 0·01M-potassium chloride being found most suitable.

Measurement of Surface Force.—After the final sharpening of the boundary, the ring was allowed to remain in the sol for 30 min. It was then raised either to the level of the boundary or just above it and allowed to hang there for 1·5 hr., to ensure complete drainage of sol from the ring. Just before the measurement was taken, the centering device was adjusted so that the suspension was clear of the sides of the constriction. The ring was then lowered into the sol by lowering the balance platform, and the balance pointer was adjusted to zero. The balance was then raised and when the ring reached the boundary the pointer was pulled downwards by the surface force.

Increasing tension was applied slowly and smoothly to the balance arm until the ring broke through the boundary, at this point the zero pointer of the balance moved sharply upwards as in an interfacial-tension measurement. After the break-through a film of lecithin could be seen, attached to the ring. The force required to achieve the break-through was read from the indicator arm of the balance and was converted into mg. by means of calibration graphs

obtained from measurements with standard weights. Repeated measurements could usually be obtained by re-sharpening the boundary by further flow from the jet (*C*).

Difficulties in the measurement of surface force. (1) If the ring was wetted by water before meeting the lecithin sol, as in the plate-pull type of cell, no surface forces could be measured. It was therefore necessary to devise a method of boundary formation such that the ring was initially wetted by the sol.

(2) If the ring was deeply immersed in the sol for 2 hr., then on raising it through the boundary only a very small surface force was found and the movement of the zero pointer of the balance was sluggish at the break-through point. This was due to adhesion of sol to the ring and its support; as it came through the boundary, it paid out this adhering sol and,

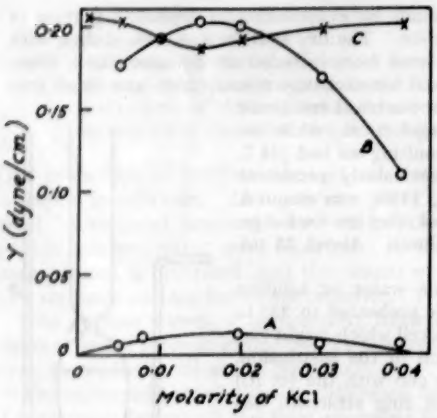


FIG. 2. *Effect of varying potassium chloride concentration on the surface force.*
A, *No bivalent metal present.*
B, $5{\cdot}6 \times 10^{-3}$M-$CaCl_2$.
C, $7{\cdot}2 \times 10^{-3}$M-$CaCl_2$.

although the ring could be seen to carry a curtain of sol up into the water layer, very little force was exerted on the ring. This difficulty was overcome by allowing a period of drainage for the ring before a measurement and also by coating the ring with a " Silicone " varnish.

(3) If the weight of the ring and suspension was too great, their inertia when set in motion upwards carried the ring through the boundary, giving low pulls with a sluggish break-through.

RESULTS

The results of the measurements of surface forces are summarised in Fig. 2—4. Equal concentrations of bivalent metal salts were present both in the sol and in the upper liquid, except where otherwise indicated. M/100-Potassium chloride was present in the sol to facilitate boundary formation. Except for those of Fig. 4, the sols all contained 0·5% w/v of lecithin. The measurements were carried out at 25° ± 0·05°.

In the absence of all small ions, which are removed by the ion-exchange treatment of the sol, the surface force at the sol–water boundary is negligible. On addition of potassium chloride to the sol a very small but measurable force of the order of 0·011 dyne/cm. is obtained (Fig. 2, *A*). A similar effect occurs with sodium chloride. Substantial surface forces are obtained in the presence of ions of bivalent metals; these ions produce forces of 0·1—0·25 dyne/cm. at concentrations of the order of 10^{-5}M.

In Fig. 3, the effect of calcium chloride on γ is shown, the graph shows two peaks: after the main peak, the value of γ falls off slowly as the salt concentration is increased. The lecithin molecule exists as a monomer only in polar organic solvents (Fauré and Legault-Demare, *Bull. Soc. Chim. biol.*, 1950, **32**, 509), and in water the sol consists of large micellar aggregates of molecules. Since the lecithin sol alone has no surface force at the boundary with water, it appears that the micelles in the boundary layer are only loosely connected together. When very low concentrations of calcium ions are introduced, a linking of micelles appears to take place as in flocculation at very low calcium concentrations, and this micellar linking results in a measurable surface force. The link is probably formed between terminal phosphate groups of adjacent micelles. Fig. 2, *C* shows

that varying potassium chloride concentration has little effect on γ at a calcium chloride concentration above that giving the main peak. Fig. 2, *B* shows that, at calcium chloride concentrations below this peak, variation of potassium chloride concentration does affect γ appreciably. In the first case (Fig. 2, *B*), the micelles are presumably completely cross-linked and further added electrolyte has little effect; in the other (Fig. 2, *C*) the cross-linking may not be complete and another electrolyte can affect the intramicellar structure.

In general form the $CaCl_2$ curve of Fig. 3 is similar to the curves published by Price and Lewis (*Biochem. J.*, **1929**, **23**, 1030) to show the effect of calcium chloride on lecithin sol–air surface tensions. The decline in γ at higher calcium concentrations is in accord with Malquoris's observations (Wittcoff, "The Phosphatides," Reinhold Publ. Corp., New York, 1951, p. 74) that very low calcium chloride concentrations cause flocculation of lecithin sols, higher concentrations peptise the colloid, and still higher cause flocculation again.

In Fig. 3, the effects of the chlorides of several bivalent metals are shown. The heights of the maxima are in the order of increasing atomic volumes of the metals Cd,

FIG. 3. *Effect of bivalent metal chlorides on the surface force.*

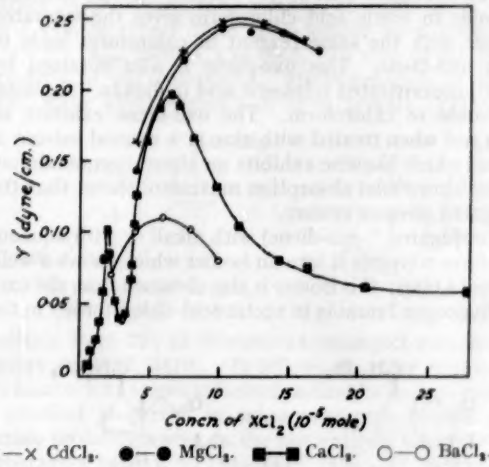
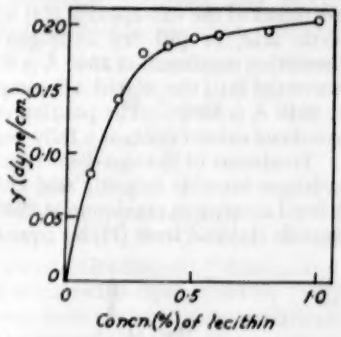


FIG. 4. *Effect of varying lecithin concentration at a fixed ratio, lecithin : XCl_2.*



Mg, Ca, Ba, but not in the same order as the ionic radii of the crystalline chlorides (Mg 0·65, Cd 0·97, Ca 0·99, Ba 1·35 Å; Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, New York, 1945, p. 346). The large effect of cadmium on γ may be due to the fact that, in addition to the cross-linking of micelles through the phosphate groups, cross-linking could also occur by a type of covalent link between the fatty acid ester groups in the lecithin molecule and the bivalent metal. The tendency of cadmium to form covalent links is well known, and the covalent nature of the lecithin–cadmium chloride complex is illustrated by its solubility in solvents such as chloroform.

Fig. 4 shows the effect of varying the concentration of lecithin in the sol at a fixed lecithin–bivalent salt ratio. γ is at first a sensitive function of lecithin concentration until at 0·3% the curve shows an abrupt change of slope; by analogy with the B.E.T. isotherm it can be supposed that at this point the boundary layer becomes completely filled with micelles giving a close-packed film.

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*Steroids. Part XV.** 22 : 23-*Dibromo*-11-*oxoergosta*-8 : 14-*dien*-3β-*yl Acetate and Related Compounds.*

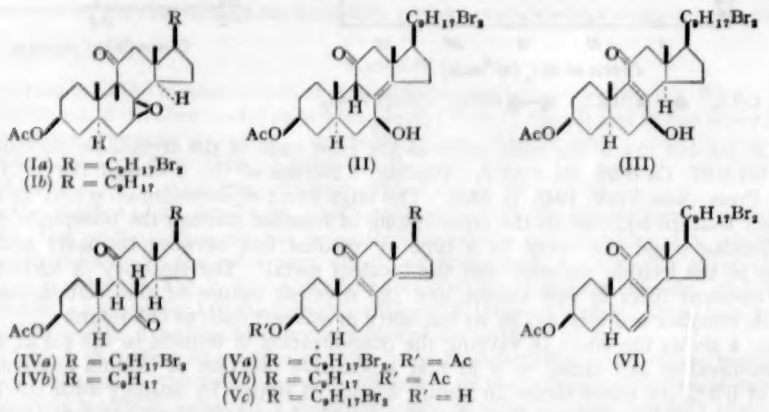
By James Grigor, G. T. Newbold, and F. S. Spring.

[Reprint Order No. 5945.]

This paper describes the preparation of a 22 : 23-dibromo-11-oxo-9β-ergostadien-3β-yl acetate which contains a conjugated diene chromophore remote from the carbonyl group. It is readily isomerised by acid or alkali to 22 : 23-dibromo-11-oxoergosta-8 : 14-dien-3β-yl acetate (V*a*), and is probably the 8(14) : 15- or 7 : 14-diene.

In Part XIV* the preparation of 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (I*a*), and its behaviour with acid and alkali, were described. On treatment with dilute sulphuric acid in dioxan it gives 22 : 23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (II), whilst with a trace of aqueous hydrogen bromide in chloroform it gives 22 : 23-dibromo-7β-hydroxy-11-oxoergost-8-en-3β-yl acetate (III). Whereas the latter with aqueous hydrogen bromide in acetic acid–chloroform gives the saturated diketone (IV*a*), treatment of the former with the same reagent in chloroform leads to dehydration and the formation of an oxo-diene. This oxo-diene is also obtained by treatment of the oxo-epoxide (I*a*) with (i) concentrated sulphuric acid in dioxan, (ii) glacial acetic acid, or (iii) dry hydrogen chloride in chloroform. The oxo-diene exhibits an absorption maximum at 2640 Å (ε 8500) and when treated with zinc in a neutral solvent is converted into the related Δ^{22}-compound which likewise exhibits an absorption maximum at 2640 Å (ε 8300). The position of the ultra-violet absorption maximum shows that the oxo-diene cannot contain a fully conjugated dienone system.

Treatment of the oxo-diene (" non-conjugated " oxo-diene) with alkali or with aqueous hydrogen bromide in acetic acid–chloroform converts it into an isomer which shows a well-defined absorption maximum at 2940 Å (ε 14,000); this isomer is also obtained from the oxo-epoxide (I*a*) and from (II) by aqueous hydrogen bromide in acetic acid–chloroform; in the

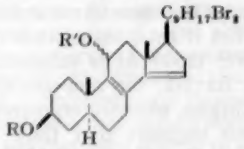


former case, 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate (IV*a*) was isolated as a second product. Debromination of the isomeric oxo-diene with zinc gives the corresponding Δ^{22}-compound which also has an absorption maximum at 2940 Å and was obtained, together with 7 : 11-dioxoergost-22-en-3β-yl acetate (IV*b*), by treatment of the oxo-epoxide (I*b*) with aqueous hydrogen bromide in acetic acid–chloroform. The location of

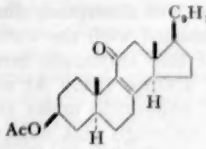
* Part XIV, *J.*, 1954, 2333.

the ultra-violet absorption maximum in the isomeric oxo-diene (conjugated oxo-diene) shows that it contains a fully conjugated dienone system, *i.e.*, that it is 22 : 23-dibromo-11-oxoergosta-8 : 14- (V*a*) or -6 : 8-dien-3β-yl acetate (VI). Reduction of the conjugated oxo-diene with lithium borohydride gives a compound considered to be 22 : 23-dibromo-ergosta-8 : 14-diene-3β : 11ξ-diol (VII*a*). Although the diol readily forms a diacetate (VII*b*) we do not on this evidence ascribe a configuration to the 11-hydroxyl group since the adjacent double bond may well affect the reactivity of this hydroxyl group. The position of the dienic chromophore in the diol is inferred from its ultra-violet absorption spectrum which shows a maximum at 2500 Å (ε 19,400) closely corresponding to that of ergosterol-B_1 (ergosta-8 : 14 : 22-trien-3β-ol, $\lambda_{max.}$ 2500 Å, ε 19,400; Fieser, Rosen, and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5397) and differing considerably from that expected for a steroid 6 : 8-diene (2750—2800 Å, ε *ca.* 10,000). It follows that the conjugated oxo-diene is (V*a*) and not (VI).

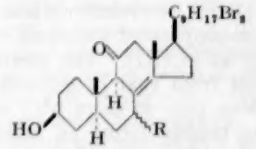
The debrominated product from the conjugated oxo-diene is consequently 11-oxo-ergosta-8 : 14 : 22-trien-3β-yl acetate (V*b*). The structure (V*b*) has been assigned by Laubach, Schreiber, Agnello, Lightfoot, and Brunings (*J. Amer. Chem. Soc.*, 1953, **75**, 1514) to a compound obtained by selective hydrogenation of 11-oxoergosta-6 : 8 : 14 : 22-tetraen-3β-yl acetate, the constants of which (m. p. 127—128·2°, $[\alpha]_D$ +20°; $\lambda_{max.}$ 2910 Å, log ε 4·06 in ether) differ considerably from those of our compound (m. p. 145—146°, $[\alpha]_D$ −2°; $\lambda_{max.}$ 2940 Å, ε 14,000). In view of this it was necessary rigidly to establish the structure of our compound. Hydrogenation of the conjugated oxo-diene over Raney nickel gave 11-oxoergost-8-en-3β-yl acetate (VIII), identical with a specimen prepared



(VII*a*) R = R′ = H
(VII*b*) R = R′ = Ac



(VIII)

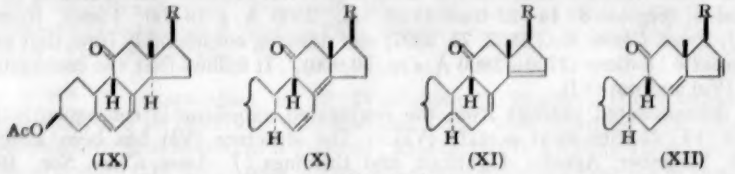


(XIII) R = 7β-OH
(XIV) R = 7α-OH

similarly from 22 : 23-dibromo-11-oxoergost-8-en-3β-yl acetate (Budziarek, Johnson, and Spring, *J.*, 1952, 3410). It follows that our compound is correctly represented by (V*b*). Dr. Laubach has since informed us that he and his colleagues have observed some variations in physical properties in subsequent preparations of 11-oxoergosta-8 : 14 : 22-trien-3β-yl acetate probably owing to the not entirely selective course of the hydrogenation; a later preparation had m. p. 140—141°, $[\alpha]_D$ +1°, in close agreement with our values, and we find that a mixture of this preparation with our sample was undepressed in m. p. We express our best thanks to Dr. Laubach for this information.

With the establishment of the structure of the conjugated oxo-diene it became possible to consider that of the " non-conjugated " oxo-diene. The fact that it gives a deep brown colour with tetranitromethane suggested that the chromophore in the " non-conjugated " oxo-diene consists of the isolated 11-carbonyl group and a conjugated diene system and not of an αβ-unsaturated carbonyl group together with an isolated double bond. The method of formation of the " non-conjugated " oxo-diene from (II) by an acid-induced dehydration also makes the latter view extremely unlikely and it was excluded by the following experiment. Treatment of the " non-conjugated " oxo-diene ($\lambda_{max.}$ 2640 Å) with lithium borohydride gave the related 11-alcohol, the ultra-violet absorption spectrum of which shows a maximum at 2610 Å (ε 11,000) thus proving that the carbonyl group is not a part of the major chromophore. As a consequence the formulæ (IX)—(XII) are to be considered for the " non-conjugated " oxo-diene. The exclusion of corresponding structures of 9α-configuration is based on the following consideration: The non-conjugated oxo-diene can only be obtained from parents with unnatural (β) configuration at $C_{(9)}$, *i.e.*, from (I*a*) or (II). Whereas treatment of 22 : 23-dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (II) with sulphuric acid gives the " non-conjugated " oxo-diene, the same treatment of 22 : 23-dibromo-11-oxoergost-8(14)-ene-3β : 7β-diol (XIII) yields the conjugated

oxo-diene, 22 : 23-dibromo-11-oxoergosta-8 : 14-dien-3β-ol (V*c*). In the latter case the configuration of the 7-hydroxyl group does not influence the course of reaction, similar treatment of 22 : 23-dibromo-11-oxoergost-8(14)-ene-3β : 7α-diol (XIV) likewise giving the conjugated oxo-diene (V*c*). A number of attempts to convert the non-conjugated oxo-diene into its 9α-epimer (cf. similar conversions described by Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, **1953**, 2921, and by Grigor, Laird, MacLean, Newbold, and Spring, *J.*, **1954**, 2333) were unsuccessful; either unchanged material was recovered or isomerisation to the conjugated oxo-diene occurred.



(IX) (X) (XI) (XII)

(R = $C_9H_{17}Br_2$)

It is difficult accurately to assess the effect, if any, of unnatural configuration at $C_{(9)}$ on the ultra-violet absorption associated with well-known steroid dienic chromophores. In our view such an effect is unlikely to be profound; then the ultra-violet absorption spectrum of the "non-conjugated" 11-oxo-diene ($\lambda_{max.}$ 2640 Å, ε 8500) is not compatible with the view that this compound is the 5 : 7- (IX), the 6 : 8(14)- (X), or the 7 : 14-diene (XI). The relatively low intensity of absorption shown by the diene chromophore in the non-conjugated oxo-diene is consonant with the view that it contains a *cisoid*-diene system as in (XI). The position of this maximum however (2640 Å) is substantially different from that of ergosteryl-B_3 acetate (2420 Å) and, further, the non-conjugated oxo-diene fails to react with maleic anhydride under conditions whereby ergosteryl-B_3 acetate readily forms an adduct. Although this behaviour suggests that the "non-conjugated" oxo-diene is probably 22 : 23-dibromo-11-oxo-9β-ergosta-8(14) : 15-dien 3β-yl acetate (XII) (and, for convenience, the compound is so named in the experimental section), we do not believe that the available evidence allows a final decision to be made with confidence. So far as we are aware a steroid 8(14) : 15-diene has not been described hitherto (cf. Lemin, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, **1953**, **75**, 1745; Fieser, Nakanishi, and Huang, *ibid.*, p. 4719).

Experimental

Specific rotations were determined in $CHCl_3$ in a 1-dm. tube at approx. 15°, and ultra-violet absorption spectra in EtOH with a Unicam S.P. 500 spectrophotometer. For chromatography, activated alumina Grade II, standardised according to Brockmann, and light petroleum, b. p. 60—80°, were used.

22 : 23-*Dibromo*-11-*oxo*-9β-*ergosta*-8(14) : 15-*dien*-3β-*yl Acetate* (XII).—(*a*) 22 : 23-Dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (I*a*) (200 mg.) in dioxan (25 c.c.) at 15° was treated with sulphuric acid (1 c.c.; *d* 1·84) and kept for 40 min. Water (10 c.c.) was added and after 1 hr. the precipitate was collected and washed with methanol. Crystallisation from chloroform–methanol gave 22 : 23-*dibromo*-11-*oxo*-9β-*ergosta*-8(14) : 15-*dien*-3β-*yl acetate* (90 mg.) as plates, m. p. 216—217°, $[\alpha]_D$ +25° (*c*, 1·1) (Found: C, 59·15; H, 7·3. $C_{30}H_{44}O_3Br_2$ requires C, 58·8; H, 7·2%). Light absorption: Max. at 2640 Å (ε 8400). It gives a red-brown colour with tetranitromethane in chloroform rapidly fading to yellow.

(*b*) A solution of the same acetate (I*a*) (1·0 g.) in dry chloroform (20 c.c.) at −5° was treated with dry hydrogen chloride for 15 min. and the solution kept for 3½ hr. The product, isolated by using chloroform, was recrystallised from chloroform–methanol, to give the previous product (XII) (220 mg.), m. p. and mixed m. p. 216—217°, $[\alpha]_D$ and absorption as before (Found: C, 58·85; H, 7·4%).

(*c*) The acetate (I*a*) (500 mg.) was treated with boiling glacial acetic acid (25 c.c.) for 2—3 min., the solution cooled, and the product precipitated by addition of water and isolated by

using ether. The solid crystallised from chloroform–methanol (mother-liquor A), to give 22 : 23-dibromo-11-oxo-9β-ergosta-8(14) : 15-dien-3β-yl acetate (XII) (200 mg.) as plates, m. p. and mixed m. p. 214—215°, $[\alpha]_D$ +24° (*c*, 1·2) (Found : C, 59·0; H, 7·35%) (absorption : as above).

(*d*) 22 : 23-Dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (II) (100 mg.) in dioxan (10 c.c.) was treated with sulphuric acid (10 drops; *d* 1·84) and kept at 15° for 40 min. Water (5 c.c.) was added and after 3 hr. the mixture gave 22 : 23-dibromo-11-oxo-9β-ergosta-8(14) : 15-dien-3β-yl acetate (XII) (40 mg.) crystallising from chloroform–methanol as plates, m. p. and mixed m. p. 217—218°, $[\alpha]_D$ +25° (*c*, 1·3) (Found : C, 58·75; H, 7·5%) (absorption : as before).

11-*Oxo*-9β-*ergosta*-8(14) : 15 : 22-*trien*-3β-*yl Acetate* (XII; but R = C_9H_{17}).—(*a*) 22 : 23-Dibromo-11-oxo-9β-ergosta-8(14) : 15-dien-3β-yl acetate (250 mg.), in a mixture of benzene (20 c.c.) ether (30 c.c.), and ethanol (30 c.c.), was refluxed with activated zinc (1·5 g.) for 4 hr. 11-*Oxo*-9β-*ergosta*-8(14) : 15 : 22-*trien*-3β-*yl acetate*, isolated in the usual manner, crystallised from chloroform–methanol as plates, m. p. 180—182°, $[\alpha]_D$ −28° (*c*, 1·1). Light absorption : Max. at 2660 (ε 8300) and 2140 Å (ε 3600) (Found : C, 79·3; H, 10·0. $C_{30}H_{44}O_2$ requires C, 79·6; H, 9·8%).

(*b*) A solution of 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (I*a*) (550 mg.) in glacial acetic acid (50 c.c.) was heated on the steam-bath with zinc (6 g.) and stirred vigorously for 2½ hr. Isolation from ether, followed by crystallisation from chloroform–methanol, gave the preceding product, m. p. and mixed m. p. 180—182°, $[\alpha]_D$ −29° (*c*, 1·8) (Found : C, 79·4; H, 9·9%). Light absorption : Max. at 2640 Å (ε 8200). A solution in chloroform gave a red-brown colour with tetranitromethane.

22 : 23-*Dibromo*-11-*oxoergosta*-8 : 14-*dien*-3β-*yl Acetate* (V*a*).—(*a*) A solution of 22 : 23-dibromo-7β : 8β-epoxy-11-oxo-9β-ergostan-3β-yl acetate (I*a*) (400 mg.) in chloroform (25 c.c.) was treated with glacial acetic acid (50 c.c.) containing aqueous 46% hydrobromic acid (10 drops) and kept overnight at room temperature. The product crystallised from chloroform–methanol, to give 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate (IV*a*), m. p. and mixed m. p. 263° (decomp.). Evaporation of the mother-liquors gave a residue, m. p. *ca.* 210° (strong yellow colour with tetranitromethane in chloroform), which was dissolved in light petroleum–benzene (1 : 1; 40 c.c.) and adsorbed on a column of alumina (10 × 1·5 cm.). The column was washed with the same solvent mixture (250 c.c.) and then with benzene (400 c.c.) which eluted a solid (120 mg.), seven crystallisations of which from chloroform–methanol gave 22 : 23-*dibromo*-11-*oxoergosta*-8 : 14-*dien*-3β-*yl acetate* (50 mg.) as plates, m. p. 221—223°, $[\alpha]_D$ +35°, +34° (*c*, 2·1) (Found : C, 59·2; H, 7·4. $C_{30}H_{44}O_3Br_2$ requires C, 58·8; H, 7·2%). It gives a bright yellow colour with tetranitromethane in chloroform. Light absorption : Max. at 2140 (ε 11,700) and 2920 Å (ε 13,700).

(*b*) Treatment of the epoxy-acetate (I*a*) with acetic acid gave a mixture from which 22 : 23-dibromo-11-oxo-9β-ergosta-8(14) : 15-dien-3β-yl acetate was isolated in 40% yield as described above. Evaporation of the mother-liquor A from this compound gave a solid (300 mg.) which was chromatographed in benzene–light petroleum (1 : 3; 100 c.c.) on alumina (15 × 2 cm.). The column was washed with benzene–light petroleum (1 : 3, 320 c.c.; 1 : 2, 250 c.c.; 1 : 1, 100 c.c.) and then with benzene–ether (19 : 1; 220 c.c.) which eluted 22 : 23-dibromo-11-oxoergosta-8 : 14-dien-3β-yl acetate (50 mg.); crystallisation from methanol gave prisms, m. p. and mixed m. p. 221—223°, $[\alpha]_D$ +35° (*c*, 0·4). Light absorption : Max. at 2130 (ε 10,000) and 2940 Å (ε 13,000). Further elution with benzene–ether (19 : 1, 370 c.c.; 17 : 3, 100 c.c.; 4 : 1, 150 c.c.; 3 : 2, 150 c.c.; 1 : 2, 250 c.c.) and ether (200 c.c.) followed by evaporation of the combined eluates and crystallisation of the residue from methanol gave 22 : 23-dibromo-7 : 11-dioxoergostan-3β-yl acetate (40 mg.), m. p. and mixed m. p. 262° (decomp.), $[\alpha]_D$ −3° (*c*, 0·8).

(*c*) 22 : 23-Dibromo-11-oxo-9β-ergosta-8(14) : 15-dien-3β-yl acetate (100 mg.) in benzene (10 c.c.) and methanolic 10% potassium hydroxide (10 c.c.) was heated under reflux for 1 hr. The product was isolated by using ether and heated on the steam-bath with acetic anhydride and pyridine for 1 hr., to give 22 : 23-dibromo-11-oxoergosta-8 : 14-dien-3β-yl acetate (50 mg.), which crystallised from chloroform–methanol as plates, m. p. and mixed m. p. 222—223°, $[\alpha]_D$ +36° (*c*, 0·7) (Found : C, 59·1; H, 7·1%). Light absorption : Max. at 2090 (ε 8000) and 2920 Å (ε 13,000).

(*d*) 22 : 23-Dibromo-11-oxo-9β-ergosta-8(14) : 15-dien-3β-yl acetate (100 mg.) in chloroform (5 c.c.) and glacial acetic acid (10 c.c.) containing aqueous 46% hydrogen bromide (10 drops) was kept at room temperature for 24 hr. Isolation by means of chloroform gave 22 : 23-dibromo-11-oxoergosta-8 : 14-dien-3β-yl acetate (60 mg.) crystallising from chloroform–methanol as

plates, m. p. and mixed m. p. 222—223°, $[\alpha]_D$ +35° (*c*, 0·4) (Found: C, 59·0; H, 7·5%). Light absorption: Max. at 2100 (ε 9000) and 2940 Å (ε 13,000).

(*e*) 22 : 23-Dibromo-7β-hydroxy-11-oxo-9β-ergost-8(14)-en-3β-yl acetate (250 mg.) in chloroform (20 c.c.) was treated with glacial acetic acid (40 c.c.) containing aqueous 46% hydrogen bromide (8 drops) and set aside at room temperature overnight. Isolation from chloroform and crystallisation from chloroform–methanol gave a solid (110 mg.), m. p. 208—211° showing absorption at 2100 (ε 9800) and 2940 Å (ε 11,100). Purification by chromatography followed by repeated crystallisation from chloroform–methanol yielded 22 : 23-dibromo-11-oxoergosta-8 : 14-dien-3β-yl acetate as plates, m. p. and mixed m. p. 219—220°, $[\alpha]_D$ +35° (*c*, 2·0). Light absorption: Max. at 2110 (ε 10,000) and 2920 Å (ε 12,500).

22 : 23-*Dibromo*-11-*oxoergosta*-8 : 14-*dien*-3β-*ol* (V*c*).—(*a*) A solution of 22 : 23-dibromo-11-oxoergost-8(14)-ene-3β : 7α-diol (XIV) (100 mg.) in dioxan (52 c.c.) and sulphuric acid (2 c.c.; *d* 1·84) was kept at room temperature for 40 min. Isolation of the product in the usual manner followed by crystallisation from chloroform–methanol gave 22 : 23-*dibromo*-11-*oxoergosta*-8 : 14-*dien*-3β-*ol* (25 mg.) as plates, m. p. 208—209°, $[\alpha]_D$ +45° (*c*, 1·5) (Found: C, 57·1; H, 7·9. $C_{28}H_{42}O_2Br_2$,2MeOH requires C, 56·8; H, 7·9%). Light absorption: Max. at 2100 (ε 10,000) and 2920 Å (ε 12,000). Acetylation gave the corresponding acetate which separated from chloroform–methanol as plates, m. p. and mixed m. p. 220—221° $[\alpha]_D$ +35° (*c*, 0·9).

(*b*) 22 : 23-Dibromo-11-oxoergost-8(14)-ene-3β : 7β-diol (XIII) (80 mg.) was dissolved in dioxan (10 c.c.) and sulphuric acid (0·4 c.c.; *d*, 1·84) and kept at room temperature for 40 min., to give 22 : 23-dibromo-11-oxoergosta-8 : 14-dien-3β-ol (35 mg.), m. p. and mixed m. p. 208—209°, $[\alpha]_D$ +47° (*c*, 0·7). Light absorption: Max. at 2100 (ε 9600) and 2910 Å (ε 11,800).

11-*Oxoergosta*-8 : 14 : 22-*trien*-3β-*yl Acetate* (V*b*).—(*a*) 22 : 23-Dibromo-11-oxoergosta-8 : 14-dien-3β-yl acetate (160 mg.) was debrominated by activated zinc (750 mg.) in ether–ethanol (50 c.c.). The product, 11-*oxoergosta*-8 : 14 : 22-*trien*-3β-*yl acetate* (90 mg.), separated from aqueous methanol as flat needles, m. p. 145—146°, $[\alpha]_D$ −2° (*c*, 1·6) (Found: C, 79·7; H, 9·8. $C_{30}H_{44}O_2$ requires C, 79·6; H, 9·8%). The compound gives a deep yellow colour with tetranitromethane in chloroform. Light absorption: Max. at 2120 (ε 8900) and 2940 Å (ε 12,500).

(*b*) 7β : 8β-Epoxy-11-oxo-9β-ergost-22-en-3β-yl acetate (I*b*) (800 mg.) in chloroform (30 c.c.) and glacial acetic acid (60 c.c.) containing aqueous 46% hydrobromic acid (12 drops) was kept overnight at room temperature. Isolation by means of chloroform and crystallisation from methanol gave a solid (500 mg.), m. p. *ca.* 130°, a solution of which in benzene–light petroleum (2 : 1, 100 c.c.) was adsorbed on a column (15 × 2 cm.) of alumina (grade II—III). Elution with benzene (50 c.c.) gave 11-oxoergosta-8 : 14 : 22-trien-3β-yl acetate (228 mg.), m. p. 143—144°, forming from aqueous methanol flat needles (180 mg.), m. p. and mixed m. p. 144—145°, $[\alpha]_D$ −3° (*c*, 3·0) (Found: C, 79·5; H, 9·8%). Light absorption: Max. at 2120 (ε 9000) and 2950 Å (ε 14,000).

Continued washing of the column with benzene (250 c.c.) and benzene–ether (200 c.c.; 19 : 1) gave a solid (130 mg.), m. p. 198°, crystallisation of which from aqueous methanol yielded 7 : 11-dioxoergost-22-en-3β-yl acetate (IV*b*) (100 mg.) as felted needles, m. p. and mixed m. p. 198—200°, $[\alpha]_D$ −30° (*c*, 1·7) (Found: C, 76·6; H, 9·85. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%).

22 : 23-*Dibromoergosta*-8 : 14-*diene*-3β : 11ξ-*diol* (VII*a*).—22 : 23-Dibromo-11-oxoergosta-8 : 14-dien-3β-ol (V*c*) (150 mg.) in tetrahydrofuran (12 c.c.) was added dropwise wth stirring during 40 min. to lithium borohydride (150 mg.) in tetrahydrofuran (15 c.c.) at 20°. Stirring was continued for 7 hr., the solution kept overnight, and the product isolated in the usual manner. Crystallisation from chloroform–methanol gave 22 : 23-*dibromoergosta*-8 : 14-*diene*-3β : 11ξ-*diol* (120 mg.), m. p. 187—188° (decomp.), $[\alpha]_D$ −18° (*c*, 1·2), −17° (*c*, 1·0) (Found: C, 56·35; H, 8·2. $C_{28}H_{44}O_2Br_2$,2MeOH requires C, 56·6; H, 8·2%). Light absorption: Max. at 2500 Å (ε 19,400). Acetylation of the diol at room temperature gave the *diacetate* (VII*b*), needles (from chloroform–methanol), m. p. 178—179° (varies with rate of heating), $[\alpha]_D$ −35° (*c*, 1·3) (Found: C, 58·5; H, 7·4. $C_{32}H_{48}O_4Br_2$ requires C, 58·5; H, 7·4%). Light absorption: Max. at 2500 Å (ε 19,600). Infra-red absorption in Nujol suspension: Acetate peaks at 1730 and 1240 cm.$^{-1}$.

11-*Oxoergost*-8-*en*-3β-*yl Acetate* (VIII).—(*a*) A mixture of 22 : 23-dibromo-11-oxoergost-8-en-3β-yl acetate (Budziarek *et al.*, *loc. cit.*) (1 g.) in benzene (150 c.c.) and Raney nickel sludge in ethanol (W7; 1 c.c.) was shaken with hydrogen until absorption was complete. Crystallisation of the product from aqueous methanol gave 11-oxoergost-8-en-3β-yl acetate (420 mg.) as blades m. p. 137—139°, $[\alpha]_D$ +122° (*c*, 0·7) (Found: C, 79·2; H, 10·9. Calc. for $C_{30}H_{48}O_3$:

C, 78·9; H, 10·6%). Light absorption: Max. at 2540 Å (ε 8600). Bladon *et al.* (*loc. cit.*) give m. p. 138—140°, $[\alpha]_D$ +119°; Laubach *et al.* (*loc. cit.*) give m. p. 137·8—138·6°, $[\alpha]_D$ +125°.

(*b*) A solution of 22 : 23-dibromo-11-oxoergosta-8 : 14-dien-3β-yl acetate (1 g.) in dioxan (150 c.c.) was shaken with hydrogen over Raney nickel (W.7; 1 c.c.) to yield 11-oxoergost-8-en-3β-yl acetate (400 mg.) as blades m. p. 137—139°, $[\alpha]_D$ +119° (*c*, 1·7). A mixture with the specimen described above was undepressed in m. p. Light absorption: Max. at 2540 Å (ε 8500).

3β-*Acetoxy*-22 : 23-*dibromo*-9β-*ergosta*-8(14) : 15-*dien*-11ξ-*ol*.—22 : 23-Dibromo-11-oxo-9β-ergosta-8(14) : 15-dien-3β-yl acetate (300 mg.) in tetrahydrofuran (60 c.c.) was treated with a solution of lithium borohydride (320 mg.) in tetrahydrofuran (25 c.c.) during 5 min. The solution was kept at room temperature overnight and the product isolated in the usual manner. Crystallisation from benzene–light petroleum gave 3β-*acetoxy*-22 : 23-*dibromo*-9β-*ergosta*-8(14) : 15-*dien*-11ξ-*ol* (130 mg.) as needles, m. p. 232° (decomp.), $[\alpha]_D$ −51° (*c*, 1·1) (Found: C, 58·7; H, 7·8. $C_{30}H_{44}O_3Br_2$ requires C, 58·6; H, 7·55%). Light absorption: Max. at 2610 Å (ε 11,400)

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The Royal Technical College, Glasgow. [*Received, December 8th*, 1954.]

The Stabilities of Metal Chelate Compounds formed by Some Heterocyclic Acids. Part I. Studies in Aqueous Solution.

By F. Holmes and W. R. C. Crimmin.

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The stability constants have been measured for some chelated compounds with metals formed by picolinic, 6-methylpicolinic, and quinoline-2- and -8-carboxylic acid in aqueous solution. The figures obtained by potentiometric titration cannot be considered as accurate but conform with the results which might be expected for these compounds. All are weak chelating agents. The complexes with *iso*quinoline-1-carboxylic acid are too insoluble for measurements to be made.

A number of reagents containing a carboxylic acid group together with a heterocyclic nitrogen atom are used in quantitative analysis, the most important being quinoline-2-carboxylic (quinaldinic), quinoline-8-carboxylic, and picolinic acid. Both the first two have been suggested as gravimetric reagents (see, *e.g.*, Flagg, "Organic Reagents in Gravimetric and Volumetric Analysis," Interscience Publ. Corp., 1948), usually for copper; for this metal Duval (*Analyt. Chim. Acta*, 1951, **6**, 47), using the thermobalance, has investigated the two systems, together with that for zinc and quinoline-8-carboxylic acid. In addition, quinaldinic acid (Majumdar and Sen, *J. Indian Chem. Soc.*, 1950, **27**, 245) and more particularly picolinic acid (*idem*, *Analyt. Chim. Acta*, 1953, **8**, 369) have been suggested as colorimetric reagents for iron. Stock (*Sborník Mezinárod. polarog. sjezdu u Praze*, 1st Congr., 1951, Part I, p. 371) has studied the behaviour of quinoline-2- and -8-carboxylic acid on polarographic reduction, comparing them with 8-hydroxyquinoline; he has investigated the possibility of amperometric titration in the cases of copper and zinc.

It is assumed that all these reagents act by forming chelated rings with metal ions, the ring being six-membered in the case of quinoline-8-carboxylic acid and five-membered in the other two cases. With these last two the ring is the same as that formed by 8-hydroxyquinoline; as, however, the dissociation constant of the carboxylic acid group

is less by several powers of 10 than that of the hydroxyl group it might be expected that correspondingly less stable complexes would be formed. Many measurements of stability constants have been made on the compounds formed by 8-hydroxyquinoline and metal ions (see, *e.g.*, Martell and Calvin, "Chemistry of the Metal Chelate Compounds," Prentice Hall, 1952), but almost none on compounds such as those listed previously and containing a carboxylic acid group. In view of this it was decided to study compounds of this type much more systematically.

The most important measurements of stability are those of Wenger, Monnier, and Epars (*Helv. Chim. Acta*, 1952, **35**, 396) in which the overall stability constant of the unstable red species formed between ferrous iron and quinaldinic acid was evaluated spectrophotometrically as $2{\cdot}6 \times 10^{-8}$, and of Majumdar and Sen (*Analyt. Chim. Acta, loc. cit.*) in which the red, soluble complex formed by ferrous iron and picolinic acid was similarly found to have an overall stability constant varying between $2{\cdot}2 \times 10^{-5}$ and $6{\cdot}4 \times 10^{-5}$ over the temperature range studied.

The compounds studied in our first investigations were picolinic, 6-methylpicolinic, quinaldinic, *iso*quinoline-1-carboxylic, and quinoline-8-carboxylic acid. All were sufficiently soluble in water for dissociation constants to be obtained therein, and all formed compounds with a wide range of metals. Some of these derivatives, as is well known, are insoluble in water; the stabilities of those which proved sufficiently soluble were determined by potentiometric titration and form the basis of this paper. A rather shorter series of metals was studied in 50% (v/v) aqueous dioxan and these results will be published separately.

Experimental

Materials.—Picolinic acid was prepared by oxidation of α-picoline by alkaline permanganate (*Org. Synth.*, 1940, **20**, 79), 6-methylpicolinic acid by Black, Depp, and Corson's method (*J. Org. Chem.*, 1949, **14**, 147), and quinoline-8-carboxylic acid according to Campbell, Kerwin, La Forge, and Campbell (*J. Amer. Chem. Soc.*, 1946, **68**, 1844). *iso*Quinoline-1-carboxylic acid was prepared by Padbury and Lindwall's method (*ibid.*, 1945, **67**, 1269), but recrystallised from hot water (Solomon, *J.*, 1947, 129); it had m. p. 168—169°, in agreement with Solomon (168—171°) but not with Padbury and Lindwall (161°). The 8-hydroxyquinoline was of B.D.H. "AnalaR" grade, and the quinaldinic acid was obtained from Messrs. Light. All these reagents were recrystallised from suitable solvents, either to constant m. p. or until only one spot was obtained on a chromatogram. Different batches of material were checked as giving identical dissociation constants.

Metals were used in the form of their perchlorates (G. Frederick Smith Co.).

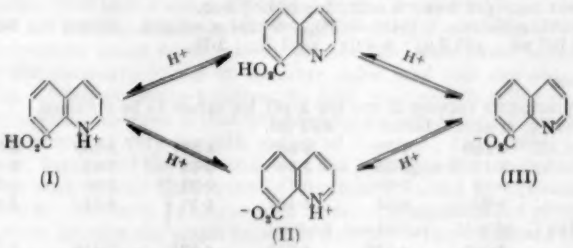
Potentiometric Titrations.—Titrations were carried out in a glass vessel of about 100 ml. capacity, provided with a Perspex cover, which was drilled with holes to admit glass and calomel electrodes, the elongated tip of a 10-ml. burette, and a jet which projected under the surface of the solution in the vessel and through which was admitted nitrogen, freed from oxygen and carbon dioxide by Fieser's solution; the nitrogen served both to stir the solution and to preserve an inert atmosphere. The vessel was kept in a thermostat at 25° ± 0·1°.

For the determination of stoicheiometric dissociation constants a measured volume of an aqueous solution of the acid was placed in the vessel, and 5 ml. of approx. 0·1N-perchloric acid were added, followed by 50 ml. of air-free water. The final solution was about 10^{-3}M with respect to the organic acid. For the determination of stability constants the water was replaced by a solution of metal perchlorate, such that the final molar concentration of the bivalent metal was half that of the organic acid.

In either case the pH of the solution was found by means of a Marconi pH meter. Carbonate-free approximately 0·1N-sodium hydroxide was then added in small portions, and the pH taken after each addition and the attainment of equilibrium. Before and after each titration the pH meter was calibrated with standard buffer solutions. The ionic strength of the solutions during titration was of the order of 0·02 and varied only slightly.

Spectrophotometric Measurements.—Absorption spectra were measured with a Unicam S.P. 500 spectrophotometer with minimum slit widths and matched 1-cm. silica cells. Hydrochloric acid was used to obtain very low pH's, acetate buffers for intermediate ones, and sodium hydroxide for higher values. The ionic strength was made constant at 0·5M with sodium chloride. The temperature was 18° ± 2°.

Results.—The acids under consideration are all dibasic, the equilibria which depend on pH being, *e.g.*:



(I) (II) (III)

For the present work it is unimportant whether form (II) is the neutral molecule, the zwitterion, or a mixture of both, but the matter will be considered in a subsequent paper. Here it will simply be assumed that the equilibria are governed by two dissociation constants. Preliminary calculations show that these in all cases are sufficiently far apart for no overlapping to occur. Hence a separate evaluation of each may be made.

Values obtained are given in Table 1. All are stoicheiometric, strictly valid only for the

TABLE 1.

Acid	First dissn. const.	Second dissn. const.	Ref.	Acid	First dissn. const.	Second dissn. const.	Ref.
Quinoline-8-carboxylic ...	2·0	6·71		Picolinic	1·5	5·43	
Quinoline-2-carboxylic ...	1·9	4·92			1·60	5·40	3
		5·0	1		1·08	5·32	4
		4·92	2			5·49	2
*iso*Quinoline-1-carboxylic	not detd.	4·97		6-Methylpicolinic	0·9	5·77	
				8-Hydroxyquinoline (for comparison)	5·00	9·70	

(1) Wenger, Monnier, and Epars (*loc. cit.*); stoicheiometric constant by pH titration at 20° and ionic strength M/30. (2) Holmes and Reed, unpublished work; stoicheiometric constants obtained spectrophotometrically at 18° ± 2° and ionic strength 0·5M. (3) Jellinek and Urwin (*J. Phys. Chem.*, 1954, **58**, 548); spectrophotometrically at 20° ± 2° and ionic strength 0·01. (4) Evans, Herington, and Kynaston (*Trans. Faraday Soc.*, 1953, **49**, 1284); apparent constants determined spectrophotometrically at 25° ± 0·1° and ionic strength 0·030M.

Stability Data for Chelated Complexes.—Concn. of NaOH used, 0·1034N; concn. of $HClO_4$ used, 0·0933N (except where otherwise stated).

I. *Quinoline-8-carboxylic acid.*

A. Copper: 0·0671N-NaOH; 0·1049N-$HClO_4$. 0·0235 g. of acid. Initial vol. 65·0 ml. NaOH, 7·360 ml.; pH 3·20; $\bar{n}$ 0·3; log 1/[L⁻] 5·3.

B. Nickel: 0·0229 g. of acid. Initial vol. 69·2 ml.

NaOH, ml.	4·583	4·720	4·861	5·024	5·164	5·310	5·451	5·548	5·660
pH	4·53	4·95	5·22	5·51	5·80	6·08	6·38	6·63	7·09
$\bar{n}$	0·13	0·32	0·56	0·74	0·89	1·07	1·23	1·31	1·35
log 1/[L⁻]	4·93	4·60	4·40	4·18	3·97	3·81	3·66	3·54	3·27

C. Cobalt: 0·0229 g. of acid. Initial vol. 68·5 ml.

NaOH, ml.	4·605	4·735	4·869	5·031	5·154	5·313	5·470	5·633
pH	5·26	5·62	5·89	6·16	6·35	6·59	6·86	7·27
$\bar{n}$	0·07	0·22	0·36	0·48	0·57	0·68	0·82	0·92
log 1/[L⁻]	4·23	3·92	3·79	3·53	3·42	3·29	3·20	3·10

D. Zinc: 0·0229 g. of acid. Initial vol. 66·8 ml.

NaOH, ml.	5·010	5·240	5·519
pH	6·36	6·70	7·16
$\bar{n}$	0·23	0·30	0·40
log 1/[L⁻]	3·30	3·11	2·95

E. Lead: 0·0229 g. of acid. Initial vol. 66·6 ml.

NaOH, ml.	4·820	4·979	5·241
pH	6·20	6·40	6·73
$\bar{n}$	0·01	0·11	0·24
log 1/[L⁻]	3·43	3·24	3·07

TABLE 1. (*Continued.*)

F. Manganese: 0·0229 g. of acid. Initial vol. 66·9 ml.
NaOH, 5·341 ml.; pH 6·84; $\bar{n}$ 0·22; log 1/[L⁻] 3·03.
G. Mercury: 0·0671N-NaOH; 0·1049N-$HClO_4$. 0·0294 g. of acid. Initial vol. 65·0 ml.
NaOH, 10·107 ml.; pH 7·62; $\bar{n}$ 0·08; log 1/[L⁻] 2·71.

II. *Quinaldinic acid.*

A. Copper: A precipitate appears at too low a pH for values to be obtained.
B. Nickel: 0·0199 g. of acid. Initial vol. 68·1 ml.

NaOH, ml.	4·140	4·520	4·666	4·861	5·050	5·381
pH	3·15	3·36	3·46	3·65	3·88	4·59
$\bar{n}$	0·23	0·58	0·71	0·91	1·05	1·38
log 1/[L⁻]	4·65	4·53	4·48	4·38	4·21	3·80

C. Cobalt: 0·0199 G. of acid. Initial vol. 68·5 ml.

NaOH, ml.	4·080	4·530	4·750	4·934	5·110	5·295	5·412
pH	3·19	3·52	3·72	3·99	4·27	4·70	5·23
$\bar{n}$	0·10	0·41	0·61	0·79	0·95	1·11	1·30
log 1/[L⁻]	4·57	4·33	4·19	3·99	3·82	3·58	3·17

D. Zinc: A precipitate forms at too low a pH.
E. Lead: 0·0671N-NaOH; 0·1049N-$HClO_4$. 0·0347 g. of acid. Initial vol. 65·0 ml.
NaOH, 8·039 ml.; pH 3·86; $\bar{n}$ 0·08; log 1/[L⁻] 3·68.
F. Manganese: 0·1122N-NaOH; 0·0149N-$HClO_4$. 0·0333 g. of acid. Initial vol. 65·0 ml.

NaOH, ml.	4·825	5·328	5·720
pH	3·82	4·43	4·81
$\bar{n}$	0·12	0·34	0·60
log 1/[L⁻]	3·72	3·25	3·08

G. Mercury: A precipitate is formed at too low a pH.

III. iso*Quinoline*-1-*carboxylic acid.*

All the metals considered are precipitated at too low a pH for measurements to be made in aqueous solution.

IV. *Picolinic acid.*

A. Copper: 0·1122N-NaOH; 0·1049N-$HClO_4$. 0·01690 g. of acid. Initial vol. 65·0 ml.

NaOH, ml.	1·950	2·100	3·160	4·200	4·560	4·923	5·202	5·560	5·688
pH	2·28	2·30	2·44	2·66	2·77	2·92	3·09	3·50	3·84
$\bar{n}$	0·74	0·83	1·20	1·45	1·55	1·65	1·69	1·76	1·81
log 1/[L⁻]	6·13	6·13	6·13	6·07	6·03	5·98	5·86	5·57	5·29

B. Nickel: 0·0174 g. of acid. Initial vol. 69·4 ml.

NaOH, ml.	2·331	3·370	4·270	4·526	4·742	4·910	5·082	5·535
pH	2·45	2·60	2·87	2·96	3·05	3·15	3·25	3·73
$\bar{n}$	0·58	0·98	1·09	1·19	1·28	1·34	1·43	1·66
log 1/[L⁻]	5·89	5·85	5·64	5·59	5·55	5·48	5·45	5·21

C. Cobalt: 0·0174 g. of acid. Initial vol. 68·9 ml.

NaOH, ml.	3·832	4·249	4·565	4·935	5·235	5·515
pH	2·77	2·90	3·05	3·27	3·56	4·13
$\bar{n}$	0·77	0·91	0·99	1·17	1·35	1·55
log 1/[L⁻]	5·60	5·50	5·39	5·26	5·08	4·68

V. 6-*Methylpicolinic acid.*

A. Copper: 0·0205 g. of acid. Initial vol. 69·6 ml.

NaOH, ml.	2·258	3·396	3·804	4·106	4·640	4·971	5·282	5·392	5·571
pH	2·42	2·61	2·71	2·80	3·01	3·24	3·59	3·80	4·31
$\bar{n}$	0·63	0·97	1·06	1·12	1·29	1·39	1·49	1·53	1·70
log 1/[L⁻]	6·26	6·20	6·14	6·07	5·96	5·93	5·53	5·37	5·06

B. Nickel: 0·0205 g. of acid. Initial vol. 69·4 ml.

NaOH, ml.	4·240	4·491	4·645	4·825	4·998	5·150	5·275	5·350	5·510	5·660
pH	3·23	3·42	3·57	3·79	4·03	4·27	4·40	4·65	5·08	5·77
$\bar{n}$	0·23	0·39	0·51	0·67	0·87	1·02	1·16	1·27	1·50	1·14
log 1/[L⁻]	5·34	5·19	5·07	4·90	4·75	4·59	4·54	4·31	4·12	3·42

C. Cobalt: 0·0205 g. of acid. Initial vol. 68·2 ml.

NaOH, ml.	4·231	4·370	4·591	4·682	4·770	4·860	4·950	5·051	5·147	5·492	5·572
pH	3·35	3·51	3·82	3·98	4·13	4·28	4·43	4·58	4·75	5·52	5·85
$\bar{n}$	0·06	0·11	0·26	0·32	0·46	0·56	0·67	0·79	0·92	1·30	1·11
log 1/[L⁻]	5·17	5·03	4·75	4·61	4·51	4·39	4·28	4·18	4·07	3·64	3·33

conditions under which they have been obtained. For all the acids considered the first dissociation constant has a pK of about 2, and at this value small errors in pH measurement can cause appreciable error in the value obtained. In the determination of stability constants, values of this order are not important to the calculation where chelation is at pH's of 4 or more. But since the compounds under consideration are chelated with some metals at pH's much less than this, it was necessary to use an accurate value, and this was obtained by spectrophotometric means. With quinoline-8-carboxylic acid, however, chelation occurred at higher values of pH, so the value recorded is that obtained by potentiometric titration.

When chelation occurs at very low pH, values of $\bar{n}$ (see *J.*, 1954, 2904) obtained may be appreciably in error, because of the importance of the hydrogen-ion concentration term in the expression for $\bar{n}$ at such pH's. Consequently $\bar{n}$ values obtained at pH $<ca.$ 2·5 have not generally been quoted. Similarly, figures at high values of $\bar{n}$ are often not given, either because precipitation occurs or because the graph indicates that no further chelation takes place.

No further metals were used with either picolinic acid or 6-methylpicolinic acid.

Discussion

It can be seen from the tables of $\bar{n}$ values that the complexes are formed at low pH's and, as already pointed out above, this may tend to a lack of symmetry in the lower part of the formation curve. For this reason, or because precipitation makes it possible to obtain only a short portion of the formation curve, formation constants cannot be evaluated in all cases and those quoted are not all of the same accuracy.

In Bjerrum's original work it is shown that the values of log $1/[L^-]$ at $\bar{n} = \frac{1}{2}$ and $\bar{n} = 1\frac{1}{2}$ may be taken as the first and second formation constants if the spreading factor is $\geqslant 10$. If this condition is not obeyed, as is the case with most of the complexes under consideration, then the values of K_1 and K_2 may be calculated from

$$\frac{\bar{n}}{(\bar{n}-1)[L]} = \frac{(2-\bar{n})[L]}{(\bar{n}-1)} K_1K_2 - K_1$$

by the method of least squares, as has been stated by Irving and Rossotti (*J.*, 1953, 3397). To obtain both K_1 and K_2 by this method, however, a reasonable portion of the formation curve must be obtained and this has not been possible in every case. Because of this, and because it was thought that the figures are not of sufficient accuracy to merit the more extensive treatment, values of log K_1, log K_2, and log $K_{av.}$ are simply values of pL for which $\bar{n} = 0{\cdot}5$, $1{\cdot}5$, and $1{\cdot}0$, respectively. In some instances it has not been possible to obtain the upper portion of the formation curve and in such cases the value of log K_2 has not been estimated from those of log $K_{av.}$ and log K_1 since with most of the compounds under present consideration it is the lower portion of the curve which is most susceptible to error. The figures obtained are given in Table 2. Nevertheless, information of some

Table 2.

	Copper			Nickel			Cobalt		
Acid	log K_1	log K_2	log $K_{av.}$	log K_1	log K_2	log $K_{av.}$	log K_1	log K_2	log $K_{av.}$
Picolinic	—	6·0	6·1	5·9	5·4	5·7	6·0	4·8	5·4
6-Methylpicolinic	6·3	5·6	6·1	5·1	4·1	4·6	4·5	3·3	3·9
Quinoline-2-carboxylic	—	—	—	4·6	—	4·3	4·3	—	3·8
Quinoline-8-carboxylic	—	—	—	4·4	—	3·9	3·5	—	—

relevance is given both by the figures and by the shape of the curves, the drop in pL with higher values of $\bar{n}$ in the case of 6-methylpicolinic acid being noteworthy as evidence of the instability of the bis-complex.

The first dissociation exponents of the parent acids are in the order quinoline-8-carboxylic = quinoline-2-carboxylic > picolinic > 6-methylpicolinic acid; and the second dissociation exponents in the order quinoline-8-carboxylic > 6-methylpicolinic > picolinic > quinoline-2-carboxylic acid. From these, it would be expected that quinoline-8-carboxylic acid would form the most stable complexes of the series since it has the highest pK in both

cases. That it does not do so could be explained in terms either of steric hindrance or of the existence of the 6-membered chelate ring (known to be in general less stable than a 5-membered ring), or of both. Very probably both effects are present but the limited range of data does not allow a distinction to be made.

Although values for log K_1 are not available in every case, the trend of log K_1 and log $K_{av.}$ is the same for both nickel and cobalt, and is: picolinic > 6-methylpicolinic > quinoline-2-carboxylic > quinoline-8-carboxylic acid. This does not follow the order of either dissociation constant. Irving and Rossotti (*J.*, 1954, 2910), when considering complexes formed by 8-hydroxyquinoline and similar compounds, showed that the second pK for the acid and log K_1 for the complex should be related, but that steric hindrance or the effect of the first acid dissociation constant might upset this relationship. With our compounds it is obvious that a simple relation between the second dissociation constant and log K_1 or log $K_{av.}$ does not exist. The effect of the first pK would be to make complexes of quinoline-2-carboxylic acid more stable with respect to picolinic acid, and those of 6-methylpicolinic acid less stable. In the latter case, however, the complexes are formed at a higher pH than corresponding ones derived from picolinic acid, and the effect of variation in the first dissociation constant in calculations of $\bar{n}$ is negligible at $\bar{n}$ values other than the lowest, a change in pK of as much as 0·6 producing little change with $\bar{n}$ values of 0·5 or more. With picolinic acid, higher $\bar{n}$ values must be attained before such changes produce negligible results, but at values of $\bar{n} = 1$ the two systems may fairly be compared for nickel and cobalt. When this is done the lower stabilities of the 6-methylpicolinic acid complexes leave no doubt that steric hindrance is operative.

In the case of quinoline-2-carboxylic acid the presence of the benzene ring in the 5 : 6-position must lead to the same effect.

All the data are in agreement with the Irving and Williams's order of stabilities (*J.*, 1953, 3192). In particular, the order is maintained with quinoline-2-carboxylic acid although the pH's of incipient precipitation of the complexes of this acid are anomalous, the nickel complex in particular being precipitated out of the expected order.

Fuller curves obtained from titration in a dioxan–water medium, to be reported later, lend support to the deductions made here.

Grateful acknowledgment is made to the University College of North Wales and the Ministry of Education for a postgraduate award to one of us (W. R. C. C.), and to the Chemical Society for a grant for the purchase of a pH meter.

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The Effect of Crystallinity on Rhythmic Precipitation.

By A. PACKTER.

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The two-dimensional precipitation of insoluble metal salts has been followed in cellulose filter-paper, and some techniques for improving crystallinity of gelatinous precipitates have been examined; improvement in this property leads to rhythmicity in the precipitation.

RHYTHMIC precipitation, first observed by Liesegang (*Z. physikal. Chem.*, 1897, **23**, 365), occurs with a wide range of insoluble materials. When a drop of concentrated silver nitrate solution is placed on a layer of gelatin gel impregnated with potassium chromate, silver chromate is precipitated, not as a continuous precipitate, but in a series of concentric rings separated by clear gel. The position of the rings follows a geometric progression law, $x_n = ak^n$, where x_n is the distance of the nth ring from the origin of diffusion; a and k are constants, k being known as the spacing coefficient (Jablczynski, *Bull. Soc. chim.*, 1923, **33**, 592).

Several hypotheses have been put forward to explain this phenomenon. Ostwald (*Z. physikal. Chem.*, 1897, **27**, 265) postulated that the material formed by metathesis is originally present as a highly supersaturated metastable solution and is precipitated only after a high degree of "supersaturation" or "supersolubility product" has been reached. According to Dhar and Chatterjee's coagulation hypothesis (*Kolloid Z.*, 1922, **31**, 15), however, the insoluble material first forms as a metastable colloidal dispersion, and precipitation occurs as a result of coagulation of this sol by excess of the diffusing ion. The latter theory received quantitative proof by Matalon and Packter (*J. Colloid Sci.*, in the press).

Although rhythmic precipitation has been generally observed in set gels, no colloid is necessary for its occurrence. Morse (*J. Phys. Chem.*, 1930, **34**, 19554), investigating the phenomenon in aqueous solution, showed that substances of all degrees of solubility and crystal habit formed periodic precipitates, when the rate of diffusion of the cation into a solution of reacting anion was sufficiently slow: the "supersaturation" or cation–anion concentration ratio at which the precipitation occurred varied from system to system. The substances showing this behaviour were all "coarsely crystalline" when precipitated in aqueous solution, and did not absorb appreciable amounts of reacting ion.

Similar results obtained by other workers have been summarised in von Weimarn's laws of precipitation (*Chem. Reviews*, 1926, **2**, 1). The average crystal size of a precipitate varied inversely as a function of the "supersaturation" of the solution from which the salt was precipitated; and crystals were not formed until the supersaturation exceeded a certain critical value. For salts such as the silver halides, a stable sol may be the most common system, obtained over a wide range of concentration of the reacting ions, and such materials do not form crystalline precipitates in aqueous media (Težak, *Discuss. Faraday Soc.*, in the press). The crystallinity of a material is thus a decisive factor in determining the rate of growth and final form of the precipitate over a wide range of "supersaturation."

In this work, Morse's experiments have been extended, and the two-dimensional precipitation of a series of insoluble metal salts has been studied in cellulose filter-papers, which have proved to be an excellent medium for such an investigation, since the high values of k obtained may be measured by simple experimental techniques; while crystalline and non-crystalline gelatinous precipitates may be readily differentiated.

The results substantiate the recent hypotheses proposed to explain the rhythmic precipitation of insoluble metal salts in set gels, and indicate clearly the importance of crystallinity in this phenomenon. A number of techniques that improve the crystallinity of gelatinous precipitates have been examined; and in all cases, improvement in this property leads to more rhythmic precipitation.

Experimental.—The following method was adopted, Whatman's No. 1 (coarse) filter-papers being used throughout. The papers (11·0 or 12·5 cm. diam.) are dipped in the anion solution (N/100—N/10), freed from excess of solution by blotting, and dried for 5 or 10 min. on a steam radiator (at 40°) to give "half-dry" or "dry" papers, respectively. A drop (0·05 ml.) of 2N-cation solution is then added at the centre of the paper, held in position, by clips, on top of glazed non-absorbent white paper, to prevent spreading. Every 2 min., a drop of distilled water is added at the same central spot. This displaces the solution, and causes the cation to travel radially through the filter paper. Under these conditions, the metal salt sol is coagulated by the cation, at cation : anion concentration ratios in the range 50 : 1.

A series of concentric rings of precipitate is generally obtained, separated by clear annuli of sol. When diffusion is complete (after 8—12 rings have been formed), the papers are dried at 40° and, where necessary for clearer definition, are developed by exposure to moist hydrogen sulphide or ammonia vapour, or sprayed with dilute solutions of these reagents. The radius of the rings is measured by reading off their distance from the centre of the paper with an accurately graduated ruler.

(I) *Direct precipitation.* The precipitation behaviour of several series of insoluble metal salts has been examined: and two main types of precipitate may be distinguished by the above technique. (*a*) Crystalline: definite crystalline particles of average size $>1\ \mu$. The excess of cation is readily washed out from the centre, and diffusion of the cation outwards leads to rhythmic precipitation. (*b*) Gelatinous: "flocculent" or "gelatinous" non-crystalline particles of average size $<1\ \mu$. The excess of cation is strongly absorbed by such a precipitate and is not readily washed out by addition of water.

With many such materials the excess of cation may itself peptise the precipitate; *e.g.*, in the precipitation of silver or cuprous iodide, the addition of distilled water leads to outward diffusion of the cation peptised sol through the paper. The results obtained are summarised in Table 1.

TABLE 1. *Type of precipitate.*

Anion	Cation (added as central drop) Crystalline	Gelatinous
Chromates	Ag^+, Cu^{++}, Pb^{++}, Hg_2^{++}, Hg^{++}	Cu^{++} (<N/50)
Iodides	Cu^+, Pb^{++}, Hg_2^{++}, Hg^{++}	Ag^+, Cu^+ (<N/50)
Arsenates	Ag^+, Pb^{++}, Hg^{++}	Cu^{++} (<N/50)
Sulphides	Ag^+, Cu^+, Hg^+, Fe^{++}, Fe^{+++}	—
Hydroxides	Ag^+, Hg_2^{++}	Cu^{++}, Pb^{++}, Fe^{+++}, Co^{++}, Ni^{++}
Silicates and thiocyanates	—	Ag^+ (N/50)

Some typical values of x_n for crystalline salts are presented in Table 2. In all cases, the spacing obeys the geometric progression law found by previous investigators, as shown by the values of x_{n+1}/x_n. It is seen that precipitation occurs at some particular cation : anion concentration ratio that may vary from salt to salt; and that rhythmic precipitation is observed only when this "supersaturation" lies within the range for which crystalline precipitates are formed.

TABLE 2. *Rhythmic precipitation in cellulose.*

Lead iodide 0·1N-I^- and 2N-Pb^{++}						Silver chromate 0·01N-CrO_4'' and 2N-Ag^+					
n	x_n, cm.	x_{n+1}/x_n	n	x_n, cm.	x_{n+1}/x_n	n	x_n, cm.	x_{n+1}/x_n	n	x_n, cm.	x_{n+1}/x_n
3	0·60	—	8	1·35	1·18	3	1·50	—	7	2·80	1·17
4	0·70	1·16	9	1·65	1·22	4	1·80	1·20	8	3·30	1·18
5	0·80	1·14	10	1·95	1·18	5	2·15	1·19	9	4·05	1·21
6	0·95	1·19	11	2·30	1·18	6	2·40	1·15	10	4·80	1·19
7	1·15	1·20	12	2·70	1·17						
					Average 1·186						Average 1·182

The spacing coefficients (values of k) may, however, vary from experiment to experiment by a factor of $\pm 5\%$, owing to small variations in the drying process. The values of $(k - 1)$ obtained for crystalline precipitates are presented in Table 3. Despite the greater rate of diffusion, the spacing is in all cases very much greater than that observed for the same materials precipitated in gelatin or carbohydrate gels (in two dimensions), where the values of $(k - 1)$ are generally <0·005. Furthermore, the spacings observed for a series of salts of a particular metal are in no way related to the solubilities of these salts in water. Similar results have been observed for three-dimensional precipitation in gelatin gels (Matalon and Packter, *loc. cit.*).

TABLE 3. *Values of* $(k - 1)$: *two-dimensional precipitation in cellulose (excess of cation).*

	0·01N-Soln.	0·1N-Soln.		0·01N-Soln.	0·1N-Soln.
Silver chromate	0·186	<0·050	Cupric pyridine thiocyanate	>0·500	0·148
,, arsenate	>0·500	0·200	,, arsenate	,,	0·200
Mercurous iodide	>0·500	0·198	Cuprous iodide	,,	0·250
,, chromate	0·094	<0·050	Lead iodide	>0·500	0·190
Ferrous ferricyanide	>0·500	0·167	,, arsenate	,,	0·150
			,, chromate	0·390	<0·050

(II) *Modification of crystallinity.* The crystallinity of the gelatinous precipitates has been modified by a number of methods.

Complexing with organic bases. Certain metal salts form highly crystalline complexes with pyridine and this fact is utilised in certain analytical methods.

(*a*) Hydroxides. Whereas papers impregnated with N-sodium hydroxide give a gelatinous central spot with most metal ions, excess of pyridine (20—30N) leads to rhythmic precipitation of, *e.g.*, ferric hydroxide as a yellow-brown precipitate : $(k - 1) = 0{\cdot}400$.

(*b*) Thiocyanates. Pyridine forms complex salts, which give crystalline precipitates, even at high "supersaturation." $Cu(CNS)_2py_2$ is rhythmically precipitated as a series of clear green rings, $(k - 1) = 0{\cdot}148$, from dry papers 0·1N with regard to CNS' and 5—10N with regard to pyridine.

Pyridine can also modify the crystallinity of many silver and copper salts by stabilising the sol against rapid coagulation at high "supersaturation" (Packter, unpublished). Silver iodide has been rhythmically precipitated as a series of pale, clear yellow rings, $(k - 1) = 0{\cdot}110$, from dry papers 0·1N with respect to I′ and 10N to pyridine; and cupric chromate and cuprous iodide give series of diffuse rings from papers 0·1N with respect to anion and 10N to pyridine.

Kolthoff (*J. Phys. Chem.*, **1932**, **36**, 860) has shown that mixed crystals may be formed when two insoluble salts are coprecipitated. The crystalline structure of a gelatinous material may be markedly modified on cellulose by coprecipitation with a second crystalline material. Two methods have been adopted.

(i) *Coprecipitation.* A mixed cation solution is diffused through papers containing the anion; or, alternatively, the cation solution may be diffused through papers soaked in a mixture of two anions. On half-dry papers, 0·1N with respect to I′, for example, outward diffusion of a mixed lead nitrate–silver nitrate solution leads to rhythmic precipitation of a very close series of clear rings of silver iodide, starting at 3·5 cm. from the centre, $(k - 1) = 0{\cdot}100$, and accompanied by the usual lead iodide rings, when the Ag^+/Pb^{++} concentration ratio $<2{\cdot}5$.

The concentration ratios of crystalline to gelatinous precipitate required to produce crystallinity and rhythmic precipitation of the latter are presented in Table 4, for a number of systems examined. (All concentrations are expressed in g.-equiv./l.) It is seen that the more crystalline lead iodide is more efficient than silver chromate in inducing crystallinity (Packter, *loc. cit.*).

TABLE 4. *Ratios of concentrations of crystalline to gelatinous precipitate required for crystallinity.*

Silver iodide:	
Coprecipitated with PbI_2	$Pb^{++}/Ag^+ = 4{\cdot}0—0{\cdot}4$.
" "	$Ag_2CrO_4 : CrO_4''/I' = 10{\cdot}0—1{\cdot}0$.
Copper chromate:	
Coprecipitated with Ag_2CrO_4	$Ag^+/Cu^{++} = 2{\cdot}5—1{\cdot}0$.

(ii) *Displacement.* A series of papers containing 8—10 rhythmically precipitated silver chromate, lead iodide, etc., rings are prepared and half dried at 40°. A third solution (N/100 cation or anion) is then diffused outwards from the centre, 0·05 ml. every 2 min. By this method silver iodide, copper chromate, etc., can be rhythmically precipitated on existent "nuclei" of a crystalline material.

Conclusions.—The above results show that cellulose is a very suitable medium for following the precipitation of many insoluble metal salts. Previous workers have already reported the use of carbohydrate media for the rhythmic precipitation of certain copper (Roy, *Kolloid Z.*, 1931, **54**, 190), lead (Hatschek, *Proc. Roy. Soc.*, 1921, *A*, **99**, 496), and magnesium (Fricke, *Z. physikal. Chem.*, 1926, **124**, 359) salts: but the protecting power of cellulose-fibre membranes is exceptionally high, and clear rhythmic precipitation with large spacing coefficients has been obtained in this medium despite the high rate of diffusion, even with such highly insoluble lead salts as the chromate. This high protection shown for such a range of metal salts allows of a quantitative investigation of precipitation behaviour by very simple techniques, and without the need for high-power optical magnification or photoelectric instruments as used by other investigators (Morse, *loc. cit.*; Veil, *Compt. rend.*, 1930, **191**, 611).

Morse's conclusion that crystallinity of the precipitated material is of fundamental importance for rhythmicity has been fully confirmed. The crystal size of precipitates of insoluble metal salts will vary inversely as the degree of supersaturation (von Weimarn, *loc. cit.*), and for "crystalline salts" such as silver chromate, lead iodide, and dipyridine-copper thiocyanate, it may be greater than 1 μ over a wide range of cation–anion concentration ratios. Precipitation that occurs at a "supersaturation" within this range then leads to formation of rings of crystalline precipitate, separated by clear peptised sol.

It also appears that the gel or membrane medium may itself affect the crystallinity of a particular insoluble salt. Gelatinous precipitates generally tend strongly to adsorb the diffusing ion as it travels through the gel or membrane. In set gels, such a material will be precipitated as a series of thick diffuse rings separated by a concentrated opaque peptised sol, and the distances cannot be measured quantitatively by simple means; while in

cellulose membranes, the insoluble material tends to be distributed throughout the medium as a peptised sol, and may hinder the displacement of the cation solution from the centre.

The crystallinity of such materials is shown to be improved by complexing with organic bases or coprecipitation with a highly crystalline material. They can then be rhythmically precipitated in cellulose, over a wide range of " supersaturation."

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The Reactions of Highly Fluorinated Organic Compounds. Part VIII. The Gas-chromatographic Separation on a Preparative Scale, and Some Reactions, of* 3H- *and* 4H-*Nonafluorocyclohexene.*

By D. E. M. EVANS and J. C. TATLOW.

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Gas–liquid partition chromatography has been applied to the separation of mixtures of volatile compounds with closely related boiling points in cases where fractional distillation is difficult. By this means, 3*H*- and 4*H*-nonafluoro*cyclo*hexene, prepared from 1*H* : 3*H*-decafluoro*cyclo*hexane by dehydrofluorination, have been separated. Further dehydrofluorination of these olefins gave the perfluoro*cyclo*hexadienes. Oxidation of the 3*H*-olefin with permanganate at 100° gave hexafluoroglutaric acid. At 80°, another acid, probably 2*H*-heptafluoroadipic acid, was obtained; when refluxed with aqueous permanganate this decomposed to give perfluoroglutaric acid. The 4*H*-olefin was oxidised to 3*H*-heptafluoroadipic acid, identical with the acid obtained previously by oxidation of crude partially fluorinated benzene mixtures.

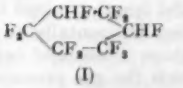
IN this paper, some further investigations of compounds derived from 1*H* : 3*H*-decafluoro*cyclo*hexane (I) (Barbour, Mackenzie, Stacey, and Tatlow, *J. Appl. Chem.*, 1954, **4**, 347) are described. Dehydrofluorination of this compound (*idem, loc. cit.*) gave nonafluoro*cyclo*hexene. Despite the narrow boiling range, it was always suspected that this product was a mixture of olefins. Subsequent isolation of perfluoro*cyclo*hexa-1 : 3- and -1 : 4-diene (Evans and Tatlow, *J.*, 1954, 3779), by exhaustive dehydrofluorination of the decafluoro-compound, confirmed this supposition. Therefore, there arose the question of fractionating these isomeric fluoro-olefins (C_6HF_9).

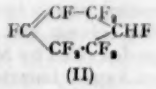
Separation of relatively small quantities of compounds having very similar boiling points, though a general problem, is particularly troublesome in organic fluorine chemistry. This is because, characteristically, fluorine compounds are very volatile, isomeric and closely related materials often have almost identical boiling points, much closer in many cases than for the hydrocarbon analogues, and azeotropes are often formed. Since, for a number of difficult separations of this sort with which we were faced, fractional distillation was not easy, owing to shortage of material, we decided to apply to the general problem the new technique of gas–liquid partition chromatography developed by James and Martin (*Biochem. J.*, 1952, **50**, 679; *Analyst*, 1952, **77**, 915). In this, the volatile mixture, in a stream of carrier gas, is passed through a tube filled with an involatile liquid adsorbed on a solid packing. Owing to differences in the partitions of components of a mixture between the gas and the liquid–solid phases, separation is effected. Hitherto, this process has been used for the analytical detection and identification of volatile compounds (James and Phillips, *J.*, 1953, 1600; Ray, *J. Appl. Chem.*, 1954, **4**, 21; 82; and others). In this work we used a general technique similar to that developed by Ray (*loc. cit.*), and our analytical columns resembled his in the most important respects. In addition, however, we have built a large column which is operated in essentially the same manner (see the

* Part VII, *J.*, 1954, 4426.

Experimental section). This column is eminently suitable for the separation and purification of quantities up to several grams of volatile compounds. Substances having boiling-point differences of as little as 1° have been separated readily, and recoveries of materials are excellent. We believe that gas–liquid partition chromatography represents an important advance not only for the identification and detection of volatile compounds, but also for work on a larger scale. It is an ideal method for the isolation and purification, etc., of volatile compounds in general organic chemistry, and particularly in fluorine chemistry.

When the nonafluoro*cyclo*hexene, prepared as described by Barbour *et al.* (*loc. cit.*), was examined in an analytical chromatographic column, small quantities of starting material (I) and of perfluoro*cyclo*hexa-1 : 3- and -1 : 4-diene, and also larger amounts of two other substances were detected. By periodic examination in an analytical column of the products of dehydrofluorinations of 1*H* : 3*H*-decafluoro*cyclo*hexane (I), suitable conditions for the production of the new compounds were established. Separation of the mixture in the larger-scale column then gave two nonafluoro*cyclo*hexenes which had boiling points about 1° apart. The structures were established by further dehydrofluorination with alkali. The lower-boiling compound gave both perfluoro*cyclo*hexa-1 : 3- and -1 : 4-diene which were identified chromatographically and then separated in turn in the large column.


(I)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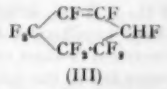
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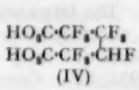
(IV)

Their boiling points and infra-red spectra were identical with those of authentic specimens. Accordingly, the parent olefin was designated 4*H*-nonafluoro*cyclo*hex-1-ene (II). The isomeric 3*H*-structure (III) was assigned to the higher-boiling olefin, since this gave with alkali only the conjugated 1 : 3-diene, identified chromatographically, by b. p. and infra-red spectrum. Oxidation of 4*H*-nonafluoro*cyclo*hexene (II) was effected with aqueous permanganate, and there was obtained 3*H*-heptafluoroadipic acid (IV), characterised as organic salts and as the diamide. These compounds had m. p.s similar to those of analogous derivatives of a heptafluoroadipic acid obtained previously (Barbour, Mackenzie, Stacey, and Tatlow, *loc. cit.*, p. 341) by oxidation of the crude mixtures of polyfluoro*cyclo*hexanes prepared by low-temperature fluorination of benzene. Accordingly, and since different acids are given by oxidation of the 3*H*-olefin (III), the 3*H*-structure (IV) has now been assigned also to the heptafluoroadipic acid which was obtained by this alternative process (*idem, loc. cit.*).

Oxidation of 3*H*-nonafluoro*cyclo*hexene (III) was attempted first under conditions similar to those used by Barbour *et al.* (*loc. cit.*, p. 341) for oxidation of the polyfluoro-*cyclo*hexane mixture. The product, isolated in moderate yield only, was hexafluoroglutaric acid, characterised as organic salts and as the diamide. When milder oxidation conditions were used, however, another acid, probably 2*H*-heptafluoroadipic acid, was obtained. Derivatives of this product were difficult to purify, but they had characteristics different from those of similar derivatives of the 3*H*-acid (IV). In particular, the dianilinium salt of the latter, used in the earlier work for purification purposes, was much less soluble than that of the former. 2*H*-Heptafluoroadipic acid, if such it was, and its derivatives seemed to be rather unstable : hence presumably the difficulty of isolation. With neutral permanganate at 100°, degradation occurred giving hexafluoroglutaric acid. Further attempts will be made later to isolate and purify derivatives of the 2*H*-acid, and then to study their reactions.

These new observations help to explain the relatively easy isolation of 3*H*-heptafluoroadipic acid (IV) from the oxidations of polyfluoro*cyclo*hexanes obtained from low-temperature fluorination of benzene. Obviously, potential precursors of the 3*H*-acid (IV) must be major constituents of the mixtures, but it now appears that any 2*H*-acid would be either decomposed in the process or removed during the purification stage. It seems likely too that small proportions of perfluoro-acids would be removed by the isolation techniques used.

Experimental

Apparatus for Gas–Liquid Partition Chromatography.—The columns used were packed with "dinonyl" phthalate (Boake, Roberts and Co. Ltd.) adsorbed on keiselguhr (Celite 545; Johns Manville Co. Ltd.) in proportions of 1 part : 2 parts respectively. This gave a good general-purpose packing for use with fluoro-compounds as with other materials. However, other high-boiling liquids such as chlorofluoro-oils, silicones, etc., appear to have useful properties for work with compounds of specific types. Nitrogen carrier gas (oxygen-free; dried by silica gel) was used throughout, the outlets being at atmospheric pressure. The issuing components were detected by thermal conductivity; changes in thermal conductivity between the ingoing nitrogen carrier gas and the issuing gas containing components were measured in a Monel-metal cell incorporating two platinum wires which were part of a Wheatstone bridge circuit. The out-of-balance potential was amplified and passed to a recording milliammeter, a peak on the chart of current against time being given by each component. Small columns (6 ft. × 4 mm. internal diameter) were used for identification of compounds as described by Ray (*loc. cit.*). Where possible authentic samples were put through under identical conditions to give reference peaks. Empirically, the times taken for compounds to pass through the column (as measured from the recorder charts) have been used as characteristics of the compounds under the particular conditions employed, the amounts present being estimated approximately from the peak heights.

The large column (16 ft. × 3 cm. internal diameter) was in two parallel lengths, joined by a short section of fine-bore capillary tubing. The column was mounted horizontally in a series of evenly wound electrical heaters of the type described by Massingham (*Chem. and Ind.*, 1951, 31). Compounds were fed to the column from a small burette in which the gas pressures could be equalised before admission. The issuing gases passed through the conductivity cell to one of a number of traps (cooled by liquid oxygen), arranged in parallel. With this column, the recorder was used merely to indicate when fractions were passing, so that each could be collected separately. The capacity of the column was dependent upon the particular mixture being fractionated. In a difficult separation, such as the one described later, about 2·5 g. was the maximum charge. If however a mixture had components with b. p.s 10—20° apart, 6—8 g. could be separated easily in some cases, since the column could be overloaded to leave only a small interval between each fraction. In general, separations were achieved more easily than with the small columns. Recoveries were virtually quantitative with no intermediate fractions. Also several azeotropes were separated without difficulty.

Nonafluorocyclohexenes from 1H : 3H-*Decafluorocyclohexane.*—The decafluoro-compound (20·0 g.; b. p. 78°, m. p. 38°), potassium hydroxide (20·0 g.), and water (100 c.c.) were refluxed together for 4 hr. When passed through the analytical chromatographic column (temperature 80°; N_2 flow rate, 1·6 l./hr.; N_2 pressure, 34 cm. Hg), a sample of the lower layer then gave 5 peaks. The first two (after 1·4 and 2·0 min.) were small ones at the same places as those given by authentic perfluoro*cyclo*hexa-1 : 4- and -1 : 3-diene, respectively, the third (at 3·25 min.) was from 4*H*-nonafluoro*cyclo*hexene, the fourth (at 3·9 min.) from 3*H*-nonafluoro*cyclo*hexene, and only a very minor fifth peak (at 5·75 min.) corresponded to that given by the pure starting material. The reaction being essentially complete, the product (13·8 g.; after being washed, dried, etc., as usual), in portions (about 2·5 g. each), was passed through the large chromatographic column (temperature 80°; N_2 flow rate, 6·8 l./hr.; N_2 pressure, 11 cm. Hg) and separated into its components. In a typical separation, the mixture (2·356 g.) gave mixed dienes (0·142 g.; being by-products these were not collected separately in this case), the 4*H*-olefin (1·601 g.), and the 3*H*-olefin (0·573 g.), the trace of starting material being allowed to escape. 4H-*Nonafluorocyclohexene* had b. p. 69°, n_D^{18} 1·311 (Found: C, 29·5; H, 0·3. C_6HF_9 requires C, 29·5; H, 0·4%), and 3H-*nonafluorocyclohexene* had b. p. 70—71°, n_D^{18} 1·311 (Found: C, 29·3; H, 0·5%).

The relative proportions of the 4*H*- and the 3*H*-olefin were varied by altering the conditions of the dehydrofluorination reaction. In general, those given above gave the highest proportion of the 3*H*-isomer, variations giving lower yields of this product. Thus, the decafluoro-compound (30·0 g.) was refluxed for 7 hr. with potassium hydroxide (9·9 g.) in water (30·0 c.c.) to give a product (21·0 g.). When a portion (2·370 g.) of this was separated chromatographically, there were obtained mixed dienes (0·180 g.), the 4*H*-olefin (1·751 g.), and the 3*H*-olefin (0·300 g.).

Dehydrofluorination of 4H-*Nonafluorocyclohexene.*—The olefin (8·45 g.), potassium hydroxide (16·8 g.), and water (16·0 c.c.) were refluxed together for 6 hr. After being washed and dried, the product (6·20 g.) was examined in the analytical chromatographic column

(temperature 80°; N_2 flow rate 1·35 l./hr.; N_2 pressure, 34 cm.) and gave two peaks (after 2·2 min. and 3·0 min.) corresponding exactly with those given by authentic samples of perfluoro-*cyclo*hexa-1 : 4- and -1 : 3-diene respectively. Separation of the mixture (3·20 g.) in the large chromatographic column gave the 1 : 4-diene (1·00 g.), b. p. 57—58°, and the 1 : 3-diene (2·10 g.), b. p. 63—64°. Infra-red measurements were made on solutions of the compounds in carbon tetrachloride (0·2—0·3M) with a Grubb-Parsons single-beam spectrometer with a rock salt prism. The 1 : 4-diene gave a single peak at 1741 cm.$^{-1}$, and the 1 : 3-diene two peaks at 1712 and 1752 cm.$^{-1}$, the total optical densities being about the same in each case. The spectra were similar to those given by authentic samples of the dienes (Evans and Tatlow, *loc. cit.*).

Dehydrofluorination of 3H-*Nonafluoro*cyclo*hexene*.—This olefin (1·37 g.), potassium hydroxide (6·0 g.), and water (6·0 c.c.) were refluxed together for 6 hr. Isolation as usual gave a product (0·54 g.) which was shown on the analytical column to be pure perfluoro*cyclo*hexa-1 : 3-diene (temperature 80°; N_2 flow rate 1·35 l./hr.; N_2 pressure 34 cm.; peak after 2·9 min.). Infra-red examination again revealed the two characteristic absorption peaks at 1712 and 1752 cm.$^{-1}$.

Oxidation of 4H-*Nonafluoro*cyclo*hexene*.—The olefin (2·50 g.), potassium permanganate (15·0 g.), and water (30 c.c.) were heated together for 17 hr. at 110—120° in a rocking autoclave. After isolation as usual there was obtained crude 3*H*-heptafluoroadipic acid (1·81 g.), m. p. 125—126°. Sublimation *in vacuo* of a portion (0·184 g.) gave the pure acid (0·150 g.), m. p. 128—130°.

The crude acid (0·298 g.) was converted in the usual manner into the dianilinium salt (0·300 g., from acetone–chloroform), m. p. 200—202° (Found: C, 47·0; H, 3·8; F, 29·0. Calc. for $C_{18}H_{17}O_4N_2F_7$: C, 47·2; H, 3·7; F, 29·0%).

This dianilinium salt (0·30 g.), in water (pH 4), was treated with *S*-benzylthiuronium chloride. The precipitate was recrystallised from water to give *di*-(S-*benzylthiuronium*) 3H-*heptafluoroadipate* (0·25 g.), m. p. 236—237° (Found: C, 43·7; H, 3·8; F, 22·0. $C_{32}H_{32}O_4N_4S_2F_7$ requires C, 43·7; H, 3·8; F, 22·0%). A sample (0·40 g.) of the heptafluoroadipic acid obtained by oxidation of a polyfluoro*cyclo*hexane mixture (Barbour *et al.*, *loc. cit.*, p. 341) was treated similarly to give the same salt (0·80 g.), m. p. 236—237°.

The dianilinium salt (0·20 g.) was refluxed for 2 hr. in ethyl alcohol (8·0 c.c.) containing commercial fluorosulphonic acid (0·2 c.c.). The mixture was poured into water, the solution extracted with ether, the extracts were dried ($MgSO_4$), filtered, and saturated with ammonia gas, and after 15 hr. the precipitate was filtered off. Recrystallisation from water afforded 3*H*-heptafluoroadipic acid diamide (0·10 g.), m. p. 205—206° (Found: C, 26·6; H, 1·9. Calc. for $C_6H_5O_2N_2F_7$: C, 26·7; H, 1·9%). M. p. values cited (*idem.*, *loc. cit.*) for the acid, dianilinium salt, and diamide were respectively 131—133°, 198—200°, and 205—206°. In each case mixed m. p.s of the samples from the two sources were unaltered, though it should be noted that depressions of m. p. are not always given on admixture of different fluoro-dibasic acids or their derivatives.

Hexafluoroglutaric Acid from 3H-*Nonafluoro*cyclo*hexene*.—The olefin (1·63 g.), potassium permanganate (12·0 g.), and water (30 c.c.) were refluxed together for 17 hr. in a flask carrying, above the water condenser, a reflux condenser cooled by solid carbon dioxide. Isolation as usual, followed by reaction with aniline in ether, gave a crude salt (0·82 g.; m. p. 212—214°). Recrystallisation from acetone–chloroform gave *dianilinium hexafluoroglutarate* (recovery 85%), m. p. 219—220° (Found: C, 48·2; H, 3·7%; equiv., 214. $C_{17}H_{16}O_4N_2F_6$ requires C, 47·9; H, 3·8%; equiv., 213). The crude salt was converted, by the methods described previously, into the *di*-(S-*benzylthiuronium*) salt (47%, from water), m. p. 188—189° (Found: C, 44·4; H, 3·9. $C_{31}H_{32}O_4N_4S_2F_6$ requires C, 44·05; H, 3·9%), and into the diamide (49%, from water), m. p. 208—209° (Found: C, 25·4; H, 1·7. Calc. for $C_5H_4O_2N_2F_6$: C, 25·2; H, 1·7%). Henne and Zimmer (*J. Amer. Chem. Soc.*, 1951, **73**, 1103) gave m. p. 209·7—210·2° for the diamide. Roylance, Tatlow, and Worthington (unpublished work) found m. p.s 218—220° and 188—190°, respectively, for dianilinium and di-(*S*-benzylthiuronium) salts of hexafluoroglutaric acid obtained from other sources.

Mild Oxidation of 3H-*Nonafluoro*cyclo*hexene*.—The olefin (0·70 g.) was treated with potassium permanganate (12·0 g.) and water (30 c.c.) for 17 hr. at 80° in a rocking autoclave. There was obtained a crude acidic product which was converted into a *dianilinium salt* (0·82 g.). After purification by recrystallisation from chloroform containing a little acetone, in which it was much more soluble than the 3*H*-isomer and the glutaric salt, this derivative (recovery 80%) shrank but did not melt at 168° and apparently had decomposed at 200° (Found: C, 46·5; H, 3·9%; equiv., 229. $C_{18}H_{17}O_4N_2F_7$ requires C, 47·2; H, 3·7%; equiv., 229). It

could not be purified further. Esterification and ammonolysis of this crude acid gave a diamide, m. p. 180—181° (Found: C, 26·9; H, 1·8. $C_9H_8O_2N_2F_7$ requires C, 26·7; H, 1·9%). The anilinium salt (0·062 g.) was converted into the di-(*S*-benzylthiuronium) salt (0·047 g., from water), m. p. 225—226° (Found: C, 43·5; H, 3·8; F, 21·4. $C_{22}H_{22}O_4N_4S_2F_7$ requires C, 43·7; H, 3·8; F, 22·0%). The production of this acid and its derivatives was not always reproducible, and the latter were difficult to purify. The specimens described above may not have been pure derivatives of 2*H*-heptafluoroadipic acid.

Action of Neutral Permanganate on the Supposed 2H-*Heptafluoroadipic Acid.*—The crude acid (0·553 g.), potassium permanganate (12·0 g.), and water (30 c.c.) were refluxed for 16 hr. Isolation as described before afforded an acidic product. This was converted into crude dianilinium hexafluoroglutarate (0·609 g.), m. p. 215—216°, which on recrystallisation from acetone–chloroform (recovery 61%) had m. p. 218—219° (Found: C, 48·1; H, 3·7%).

The authors thank Professor M. Stacey, F.R.S., for his interest, and Drs. A. J. P. Martin, F.R.S., and A. T. James, and Mr. N. H. Ray for extremely helpful discussions. Gratitude is also expressed to the D.S.I.R. for a maintenance award (to D. E. M. E.), to Mr. R. Worrall for the infra-red measurements, and to Mr. W. E. Massingham and Mr. N. S. Bradford for construction of apparatus.

THE CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

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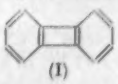
Heats of Combustion and Molecular Structure. Part III. Diphenylene.*

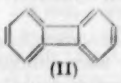
By R. C. CASS, H. D. SPRINGALL, and (in part) P. G. QUINCEY.

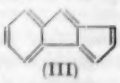
[Reprint Order No. 5847.]

The heat of combustion and vapour pressure of diphenylene have been measured. The resonance energy of this compound has been calculated and is considered in terms of its structure.

DIPHENYLENE was first synthesised by Lothrop (*J. Amer. Chem. Soc.*, 1941, **63**, 1187). The synthesis was confirmed by Baker (*Nature*, 1942, **150**, 210), who has also reviewed the earlier work (*J.*, 1945, 265), reported an improved synthesis, and described further reactions of this compound (Baker, Boarland, and McOmie, *J.*, 1954, 1476). The dibenzo-*cyclo*butadiene structure (I) for diphenylene was advocated by Lothrop and later investig-


(I)


(II)


(III)

ations, notably the complete *X*-ray crystal structure analysis by Waser and Chia-Si Lu (*J. Amer. Chem. Soc.*, 1944, **66**, 2035), conclusively established its correctness. It seemed desirable to investigate thermochemically the energetics of this interesting structure.

EXPERIMENTAL

Materials.—The benzoic acid used for the determination of the water equivalent of the calorimeter was of B.D.H. thermochemical standard grade, and the succinic acid used to check the calibration was of "AnalaR" grade. Both were stored over phosphoric oxide for several weeks before use. The diphenylene (2·9 g.), recrystallised from methanol and having m. p. 110—111°, was made available to us by Professor W. Baker, F.R.S., and was used without further purification. The density of diphenylene (1·21 ± 0·02 g./c.c.), needed for vacuum correction of weights, was determined by flotation in potassium iodide solution. Waser and Chia-Si Lu (*loc. cit.*) have reported a value of 1·24 g./c.c., using a sublimed sample.

Latent Heat of Sublimation.—The vapour pressure of diphenylene was measured over the range 98—108°, using an apparatus of the type described by Sanderson ("Vacuum Manipulation of Volatile Compounds," Wiley, New York, 1948, p. 84), the temperature being controlled to

* Part I, *Trans. Faraday Soc.*, 1954, **50**, 815; Part II, *J.*, 1954, 2764.

within ±0·1°. For this range it was expressed by the equation $\log_{10} p_{mm} = -6755{\cdot}53/T + 18{\cdot}26$, from which the latent heat of sublimation was evaluated as 30·8 kcal./mole. The value at 25°, which could not be measured in our apparatus owing to the involatility of diphenylene at that temperature, may be assumed to be almost identical with that at the higher temperature (cf. Sidgwick, "The Covalent Link in Chemistry," Cornell Univ. Press, Ithaca, 1933, pp. 103—105).

Combustion Apparatus and Procedure.—The combustion apparatus described by Springall, White, and Cass (*Trans. Faraday Soc.*, 1954, **50**, 815) was used for this work with the following modifications. The Beckmann thermometer previously used to record the temperature rise during a combustion was replaced by a platinum resistance thermometer, the change of resistance, ΔR, being measured by means of a Smith's difference bridge (*N.P.L. Collected Researches*, 1913, **9**, 219). Temperature differences were measured with an accuracy of ±0·0002°. The temperature conditions under which the combustions were carried out differ from those described previously in that the room temperature, for this work, was controlled at 25·00° ± 0·05° and the circulating water at 28·000° ± 0·003°.

The combustion procedure followed in this work also differs slightly from that previously described. The variable value for the water equivalent of the calorimeter used in our earlier work, expressed as $E' = E + k\theta_m$, where θ_m is a "mean temperature" defined as $\theta_{10} + \Delta\theta/2$ (θ_{10} and $\Delta\theta$ being, respectively, the temperature at the time of ignition and the corrected temperature rise), is due to the variation of θ_{10}. It has been shown, as a result of thirty benzoic acid combustions, that for $\Delta\theta$ lying in the range 1·3—2·5° the water equivalent is constant, within the experimental limits of aaccuracy, provided that θ_{10} is constant. We therefore now carry out the combustions at the same firing temperature to within ±0·0002°. A 2-w heater was inserted in the calorimeter in order to reduce the time taken for the calorimeter to attain the firing temperature.

It was also found that by flushing out the bomb six times with oxygen at 10 atm. instead of twice, as in the previous work, the nitric acid correction for nitrogen-free compounds was considerably reduced.

The water equivalent (E) of the calorimeter was determined by using benzoic acid pellets, the mean value from ten combustions being 31199·0 ± 8·0 cal./ohm.

The calibration was checked by measuring the heat of combustion of succinic acid, three samples of which were burnt immediately before and three immediately after the experiments using diphenylene. The results of these two sets of combustions were identical, the value being $-\Delta U_b = 356{\cdot}63 \pm 0{\cdot}08$ kcal./mole. This value is in good agreement with those obtained by other workers, *viz.*, 356·68 ± 0·05 (Bechers and Roth, *Z. physikal. Chem.*, 1937, **179**, *A*, 450; and Huffman, *J. Amer. Chem. Soc.*, 1938, **60**, 1171) and 356·69 ± 0·06 kcal./mole (Pilcher and Sutton, personal communication).

The amount of diphenylene available permitted the burning of only four samples. The first two, with normal sized fuses, unfortunately failed to burn completely. The final two combustions were made cleanly by using comparatively large fuses of 0·0436 and 0·0177 g. of filter paper.

Results.

The results of the last two diphenylene combustions are tabulated.

Heat of combustion of diphenylene ($M = 152{\cdot}18$).

m (vac.) (g.)	ΔR (ohms)	Corrections (cals.): fuse	HNO_3	carbon	C (cal./ohm)	$-\Delta U_b$ (kcal./mole)
0·6171(7)	0·19771	173·96	0·08	1·57	4·3	1478·55
0·7477(3)	0·23591	70·62	0·21	1·58	4·3	1483·73

$-\Delta U_b = M/m[(E + C)\Delta R - \text{corr.}_{\text{fuse}} - \text{corr.}_{HNO_3} + \text{corr.}_{\text{carbon}}] \times 10^{-3}$ kcal./mole.

Mean value $-\Delta U_b = 1481{\cdot}1_4$ kcal./mole.
Standard deviation ($-\Delta U_b$) = 0·12%
Overall uncertainty interval = 0·16$_5$%
Washburn correction (w) = 0·95 kcal.
$\Delta nRT = -1{\cdot}20$ kcal.
$-\Delta H_c^\circ = 1481{\cdot}4 \pm 2{\cdot}5$ kcal./mole (from $-\Delta H_c^\circ = -\Delta U_b - w - \Delta nRT$)

The value for $-\Delta H_c^\circ$, derived from only two combustion experiments, is subject to much wider limits of error than is usual. Unfortunately, no more of the valuable and rather inaccessible diphenylene can be made available. In view of the very interesting structural

questions involved, we have therefore proceeded with the theoretical consideration of the problem, bearing in mind the restrictions imposed by the scantiness of the data, and using $-\Delta H_c^\circ = 1481 \pm 5$ kcal./mole.

Discussion.

The dibenzo*cyclo*butadiene structure, containing a four-membered ring, must be considerably strained. Lothrop (*loc. cit.*) suggested that the Mills–Nixon effect might stabilise the molecule in the form (II). This, however, seems unlikely as the four carbon atoms which constitute the four-membered ring must be of the same trigonal planar (sp^2) type in both (I) and (II). Coulson (*Nature*, 1942, **150**, 577) reported calculations indicating that the destabilising strain energy of (I) was approximately 100 kcal./mole, whereas that of the isomeric *cyclo*pentindene (III) was only a few kcal./mole, although the total resonance stabilisation energies of both structures were nearly the same (90 and 86 kcal./mole respectively).

After the experimental establishment of structure (I) for diphenylene, the high theoretical value for the strain energy of this structure reduced. In a recalculation on *cyclo*butadiene, using the concept of "bent" bonds, Coulson and Moffitt (*Phil. Mag.*, 1949, **40**, 26) evaluated the strain energy per CH group, due to σ-bonding, as 0·8 ev. On the assumption that these results can be applied directly to the four-membered ring of diphenylene, the calculated strain energy for this compound becomes ~74 kcal./mole.

Our work was undertaken to assess experimentally the strain conditions in the established structure. This is most simply done by comparing the net molecular resonance energy, E_r, for diphenylene with that for diphenyl.

E_r for diphenylene was evaluated from our $-\Delta H_c^\circ$ and L_g^{st} values, using the method and accessory thermochemical data of Part I (*loc. cit.*). The value thus obtained for the E_r term is 22 ± 5 kcal./mole. For diphenyl, $-\Delta H_c^\circ$ is 1493·3 kcal./mole (Parks and Vaughan, *J. Amer. Chem. Soc.*, 1951, **73**, 2380). The corresponding L_g^{st} term is 17·4 kcal./mole (Bright, *J.*, 1951, 624). These values, together with the same accessory data as were used for diphenylene, yield for diphenyl, $E_r = 81{\cdot}4$ kcal./mole.

These two E_r terms indicate that the closing of the *cyclo*butadiene ring system in the transformation of diphenyl into diphenylene is accompanied by a destabilisation (strain energy) of 59 ± 5 kcal./mole. The degree of agreement between this experimental value and the value forecast in the second theoretical approach by Coulson and Moffit is encouraging.

We thank Professor W. Baker, F.R.S., for the gift of diphenylene used in this work.

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Synthesis of 2 : 3-6 : 7-*Dibenzofluoranthene.*

By Neil Campbell, Angus Marks, and G. V. McHattie.

[Reprint Order No. 5848.]

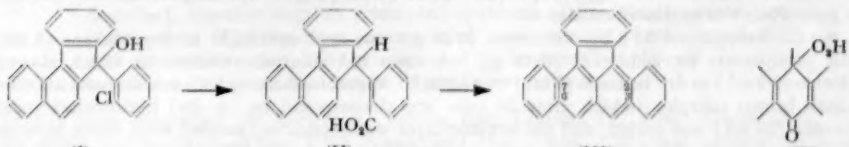
2 : 3-6 : 7-Dibenzofluoranthene has been synthesised and identified with the hydrocarbon obtained by Clar and Stewart (*J.*, 1952, 4783).

The synthesis of 2 : 3-6 : 7-dibenzofluoranthene (III) has been effected by condensing 3 : 4-benzofluorenone with the Grignard reagent prepared from *o*-bromochlorobenzene to give the alcohol (I). By standard methods this was converted into the carboxylic acid (II), the acid chloride of which on treatment with stannic chloride gave a mixture from which a very small yield of 2 : 3-6 : 7-dibenzofluoranthene (III) was obtained chromatographically. Dr. Clar kindly proved it to be identical with the hydrocarbon which he had obtained by different methods (Clar and Stewart, *loc. cit.*). The formation of the hydrocarbon rather than the anthrone was unexpected (see, *e.g.*, Campbell and Marks, *J.*, 1951, 2941). On another occasion the product was a peroxide, whose structure we were unable to investigate in detail, but which we regard as a hydroperoxide (IV) in view of the analogous hydroperoxide formation by the action of oxygen on 9-phenylanthranol or an alkaline

solution of 9-phenylanthrone (Dufraisse, Etienne, and Rigaudy, *Bull. Soc. chim. France*, 1948, 804).

It is to be noted that ring-closure (II ⟶ III) may take another course and a more detailed investigation may reveal some 2 : 3-10 : 11-dibenzofluoranthene or its derivatives among the products.

2 : 3-6 : 7-Benzofluoranthene forms an adduct with maleic anhydride and is rapidly oxidised on an alumina column to give a peroxide. From the parallelism between maleic



(I) (II) (III) (IV)

anhydride adduct formation and the photo-oxidation of anthracene derivatives we suggest that the peroxide is the transannular photoxide of the benzofluoranthene and it is pertinent that 9 : 10-dimethyl-1 : 2-benzanthracene is rapidly oxidised chromatographically on alumina to give a photo-oxide (Sandin and Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 3098; Cook and Martin, *J.*, 1940, 1125; Cook, *Ann. Reports*, 1942, **39**, 189).

In other attempts to synthesise the dibenzofluoranthene, 1-benzoyl-9-phenyl-3 : 4-benzofluoren-9-ol and 3 : 4-benzofluorene-1-carboxylic acid were prepared.

Experimental

M. p.s were determined on the Kofler block; chromatographic purification was effected on alumina; and fluorescence observations were made under a Hanovia ultraviolet lamp.

9-o-*Chlorophenyl*-3 : 4-*benzofluorene*-9-*ol*.—Boiling phenylpropiolic acid with acetic anhydride for 5—6 hr. or acetic acid–acetic anhydride (4 : 1) for 2—3 hr. gave consistent 55—60% yields of 1-phenylnaphthalene-2 : 3-dicarboxylic anhydride. Schaarschmidt's 78% yield (*Ber.*, 1915, **48**, 1826) could not be repeated. Ring-closure gave 3 : 4-benzofluorenone-1-carboxylic acid, which was best decarboxylated in boiling quinoline with copper. Chromatographing the product gave 3 : 4-benzofluorenone (70—80%), m. p. 159—160°, giving a green colour with concentrated sulphuric acid.

3 : 4-Benzofluorenone (11·5 g.) in dry benzene (250 ml.) was added to the Grignard reagent (4 mol.) prepared from *o*-bromochlorobenzene (24 ml.) and magnesium (4·7 g.) in ether (700 ml.), the solution then being boiled for 12—15 hr. After decomposition with ice and hydrochloric acid, the organic layer was separated and on evaporation yielded an oil. Trituration with light petroleum gave 9-o-*chlorophenyl*-3 : 4-*benzofluoren*-9-*ol* (65%) as a solid, prisms (from ethanol), m. p. 100° (decomp.) followed by solidification, the anhydrous substance melting at 170° (Found : C, 76·4; H, 5·0; Cl, 9·6. $C_{23}H_{15}OCl,H_2O$ requires C, 76·4; H, 4·7; Cl, 9·7%). The anhydrous *compound* was obtained by drying at 80° (Found : C, 80·2; H, 4·1; Cl, 10·6. $C_{23}H_{15}OCl$ requires C, 80·6; H, 4·3; Cl, 10·3%). It gives a red colour with concentrated sulphuric acid.

2 : 3-6 : 7-*Dibenzofluoranthene*.—The above alcohol (11·9 g.) was boiled for 3 hr. with amalgamated zinc (10 g.), zinc dust (5 g.), and concentrated hydrochloric acid. Zinc dust (2 g.) was added and boiling continued for a further 1 hr. The solution was poured into water, and the precipitate, dissolved in benzene, was chromatographed. A strong blue fluorescent zone developed and yielded an oil which solidified on trituration with light petroleum. 9-o-*Chlorophenyl*-3 : 4-*benzofluorene* (82%), prisms (from light petroleum), had m. p. 106—107° (Found : Cl, 11·5. $C_{23}H_{15}Cl$ requires Cl, 10·8%). This substance (8·6 g.), cuprous cyanide (3·6 g.), pyridine (20 ml.), and acetonitrile (2 ml.) were heated in a sealed tube for 24 hr. at 240°. The mixture was poured into dilute hydrochloric acid and extracted with benzene, and the benzene washed with aqueous ammonia, water, acid, and water, and dried. The solution was passed down a column and when developed with benzene yielded a pale yellow band from which 9-o-*cyanophenyl*-3 : 4-*dibenzofluorene* (74%) was obtained as an oil which solidified when triturated with light petroleum and crystallised from benzene–light petroleum in prisms, m. p. 140° (Found : N, 4·1. $C_{24}H_{15}N$ requires N, 4·4%).

The cyano-compound (2·0 g.) in acetic acid (18 ml.), concentrated sulphuric acid (9 ml.), and

water (18 ml.) was boiled for 18 hr. and the whole poured into water. 9-o-*Carboxyphenyl*-3 : 4-*benzofluorene* separated and was extracted with warm aqueous sodium carbonate. Acidification and crystallisation from acetic acid (charcoal) gave needles (0·9 g.), m. p. 200° (clear only at 225°) (Found : C, 85·0; H, 5·3. $C_{24}H_{16}O_2$ requires C, 85·7; H, 4·8%). A quantitative hydrolysis was effected by boiling (24 hr.) the cyano-compound (3·5 g.), sodium hydroxide (1·4 g.), water (3·5 ml.), and ethylene glycol (17·5 ml.). Pouring the mixture into acidified water gave the acid. It formed a *methyl ester*, nodules (from light petroleum), m. p. 110—111° (Found : C, 85·2; H, 5·3. $C_{25}H_{18}O_2$ requires C, 85·7; H, 5·2%). The m. p. of the acid obtained by hydrolysis was as described above.

9-o-Carboxyphenyl-3 : 4-benzofluorene (0·34 g.) was kept overnight in dry benzene (5 ml.) with phosphorus pentachloride (0·35 g.). A deep red solution resulted to which stannic chloride (0·2 ml.) in dry benzene (3 ml.) was added. Vigorous shaking for a few minutes afforded a dark brown complex, which after 30 min. was decomposed by ice and hydrochloric acid. Benzene (25 ml.) was added, and the organic layer was separated, washed with dilute aqueous sodium carbonate, dried (Na_2SO_4), and concentrated. The wine-red concentrate was chromatographed. The column was developed with benzene, then sealed off overnight, and a bluish-green band at the top with a greenish-yellow fluorescence was extracted with acetone, which on evaporation yielded a product whose analysis and properties indicated that it was the *hydroperoxide* of 1 : 9-o-phenylene-2 : 3-benzanthrone, needles (by sublimation at 210°), m. p. 235—239° (decomp.) (Found : C, 82·3; H, 4·4. $C_{24}H_{14}O_3$ requires C, 82·3; H, 4·0%). It gave a positive oxidation test with ammonium thiocyanate and ferrous ammonium sulphate in acetone and concentrated sulphuric acid.

9-o-Carboxyphenyl-3 : 4-benzofluorene (1 g.) was suspended in dry benzene (10 ml.), and phosphorus pentachloride (0·9 g.) was added. The suspension was gently warmed and after the solid acid had disappeared (15 min.) stannic chloride (0·4 ml.) in dry benzene (6 ml.) was added. The solution overnight deposited a dark-brown complex which was decomposed and worked up as above. A wine-red band with a vermilion fluorescence separated on the column and on extraction yielded 2 : 3-6 : 7-dibenzofluoranthene (0·06 g.), purple needles (from acetic acid), m. p. or mixed m. p. 215—218° (Found : C, 94·5; H, 4·9. Calc. for $C_{24}H_{14}$: C, 95·3; H, 4·7%).

In another experiment, carried out as above except that after addition of the stannic chloride the mixture was kept for 20 hr. before being decomposed, the product was chromatographed, giving two zones from the lower of which some dibenzofluoranthene was obtained. The upper green zone with a greenish-yellow fluorescence gave a yellow powder, which was again chromatographed. The prominent yellow zone (green on the side exposed to light) was extracted with benzene–chloroform, evaporation of which yielded the *photo-oxide* of 2 : 3-6 : 7-dibenzofluoranthene, colourless needles (from toluene), decomp. 260° (Found : C, 85·6; H, 4·3. $C_{24}H_{14}O_2$ requires C, 86·2; H, 4·2%). It gave positive tests for an oxidising agent.

Attempted Preparation of Methyl 9-*Hydroxy*-9-*phenyl*-3 : 4-*benzofluorene*-1-*carboxylate*.—The action of phenylmagnesium bromide on methyl 3 : 4-benzofluorenone-1-carboxylate was studied under various conditions, but only one experiment gave a pure product. The ester (0·78 g.) in dry benzene (30 ml.) was added to excess of Grignard reagent prepared from bromobenzene (2·35 ml.) and magnesium (0·55 g.) in anhydrous ether (100 ml.), and the whole was boiled for 10 hr. Decomposition of the product with ice and hydrochloric acid followed by evaporation of the ether gave an oil (0·55 g.), which when triturated with light petroleum gave 1-*benzoyl*-9-*phenyl*-3 : 4-*benzofluoren*-9-*ol*, colourless prisms (from ethanol–benzene), m. p. 243—245° (Found : C, 86·8; H, 4·9. $C_{30}H_{20}O_2$ requires C, 87·4; H, 4·9%). It gives a wine-red colour with concentrated sulphuric acid.

3 : 4-*Benzofluorene*-1-*carboxylic Acid*.—Methyl 3 : 4-benzofluorenone-1-carboxylate (0·5 g.) was boiled for 4½ hr. with lightly amalgamated zinc (0·6 g. of metal; 0·6 g. of dust), toluene (15 ml.), acetic acid (50 ml.), and hydrochloric acid (10 ml.), toluene being added to dissolve crystals which separated. The organic layer was separated, dried (Na_2SO_4), and reduced to half volume. On cooling, 3 : 4-*benzofluorene*-1-*carboxylic acid* (0·27 g.) separated; it formed colourless needles (from toluene), m. p. 322—325° (rapid heating) (Found : C, 82·8; H, 4·6. $C_{18}H_{12}O_2$ requires C, 83·1; H, 4·6%).

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The Fine Structure of Azulene. Part I. cyclo*Hepta*[bc]*acenaphthylene and* cyclo*Hepta*[def]*fluorene.*

By D. H. Reid, W. H. Stafford, and J. P. Ward.

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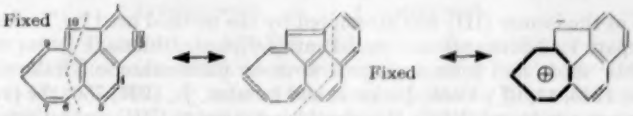
A synthesis of *cyclo*hepta[*bc*]acenaphthylene (II) from acenaphthene is described, together with an attempted synthesis of the isomeric *cyclo*hepta-[*def*]fluorene (III) by ring expansion of *cyclo*penta[*def*]phenanthrene (IV) with diazoacetic ester. The properties of the hydrocarbon (II) are discussed, together with the unusual results of the latter synthesis.

It has been suggested by Anderson, Nelson, and Tazuma (*J. Amer. Chem. Soc.*, 1953, **75**, 4980) and by Stafford and Reid (*Chem. and Ind.*, 1954, 277) that azulene (I) is best represented as a resonance hybrid of two types of canonical forms, (*a*) the classical covalent forms and (*b*) betaine structures. In the latter the cationic character is associated with

(I*a*) (I*b*) (I*c*)

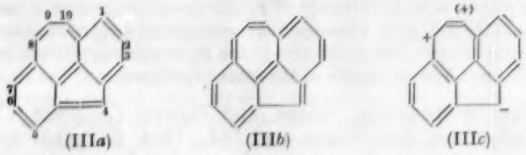
the seven-membered ring and the anionic character equally with the equivalent 1- and 3-positions in the five-membered ring. This formulation interprets the reactions of the azulenes and includes them within the class of anhydro-salts which Galloway, Reid, and Stafford (*Chem. and Ind.*, 1954, 724) have indicated often possess comparable colour and reactivity because of a highly dipolar character. On this basis azulene is an aromatic system with the unusual features that two positions possess a high electron density balanced by an attenuation of the π-electron density in the seven-membered ring. One typical property is the ready polarisability of the system; in appropriate circumstances an electron pair may be developed on either $C_{(1)}$ or $C_{(3)}$ and shared with an electrophilic group. The basicity of the azulenes manifests both this polarisability and the stability of the polarised state once the electrons have been shared, *i.e.*, it reflects the stability of the corresponding *cyclo*pentadienyl*cyclo*heptatrienylium ion (I*c*). These criteria, the polarisation of the ground state and the ready polarisability to an excited state, with their corollaries of colour and basicity, represent an efficient method of identifying typical azulenic character, for this is synonymous with considerable contribution of betaine forms



(II*a*) (II*b*) (II*c*)

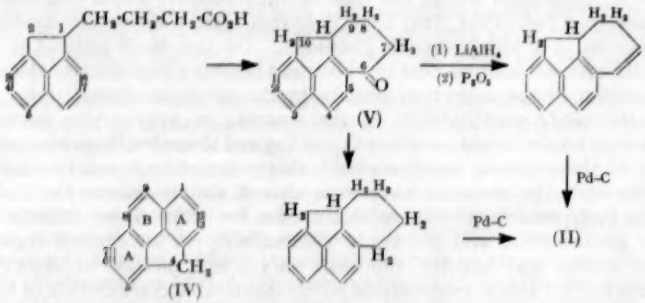
1 : 2-Benzazulene is the only azulene so far synthesised and studied which possesses only one chemically recognisable position for the adoption of anionic character, so similar systems in which the five-membered ring is more closely enveloped deserve study. Two structures were selected for a preliminary examination, *cyclo*hepta[*bc*]acenaphthylene (II) and *cyclo*hepta[*def*]fluorene (III). These are both capable of representation as *cyclo*polyolefins but if all reasonable structures, both of covalent and of betaine type, are written then differences are obvious. Covalent structures for (II) are represented by (II*a* and *b*), in which, respectively, the classical naphthalene and azulene forms all contribute with the fixed bond structure indicated in the remaining portion of the molecule, thereby giving five reasonable covalent canonical forms. The betaine structures are, in part, represented by (II*c*), in which the seven-membered ring donates an electron to $C_{(10)}$ while the naphthalene portion may again be written as varying in the normal manner.

The source of the enhanced electron-density at $C_{(10)}$ should also include the naphthalene portion. For the compound (III) there are only two purely covalent forms, (III*a* and *b*), in neither of which the diphenyl or azulene structural type is preserved. Both involve complete double-bond character for the central bond. Betaine contributants are also limited to two structures (III*c*) in which only positions 8 and 10 may act as electron sources. It would therefore be expected that a hydrocarbon of structure (II) would be typically azulenic, whereas one of structure (III) would be a typical *cyclo*polyolefin.



(III*a*) (III*b*) (III*c*)

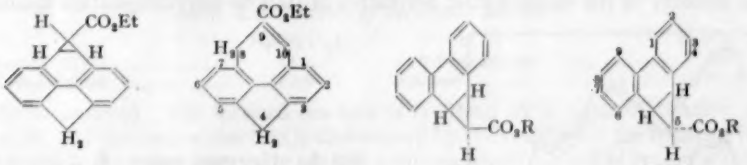
The hydrocarbon (II) was synthesised from γ-1-acenaphthenylbutyric acid (cf. Bachmann and Sheehan, *J. Amer. Chem. Soc.*, 1941, **63**, 204) which was prepared from 1-acenaphthenylacetic or preferably from β-1-acenaphthenylpropionic acid by the Arndt–Eistert reaction. Ring-closure, by polyphosphoric acid, of the butyric acid gave 6 : 7 : 8 : 9-tetrahydro-6-oxo*cyclo*hepta[*bc*]acenaphthene (V) in excellent yield, which is best converted into the desired product (II) by successive reduction with lithium aluminium hydride, dehydration to 8 : 9-dihydro*cyclo*hepta[*bc*]acenaphthene, and dehydrogenation. The azulene was isolated by extraction into syrupy phosphoric acid followed by dilution, and was obtained as dark red leaflets which form a trinitrobenzene complex.



Synthesis of the isomer (III) was attempted by the method used by Treibs (*Ber.*, 1948, **81**, 38) to prepare 1 : 2-benzazulene. *cyclo*Penta[*def*]phenanthrene (IV) was made to react with diazoacetic ester, and from analogous work on phenanthrene (Drake and Sweeney, *J. Org. Chem.*, 1946, **11**, 67; Cook, Dickson, and Loudon, *J.*, 1947, 750) the product should be a *cyclo*propane compound (VI*a*); this should rearrange to (VI*b*) and on dehydrogenation then give an ester derived from (III). In fact two esters which were azulenic (extractable into phosphoric acid) were isolated and both on hydrolysis and decarboxylation yielded the isomer (II). Substantial attack must have occurred in ring A and presumably on the 1 : 2- and 2 : 3-bonds in that ring. The significance of this is discussed below. The material which was not extractable into phosphoric acid was separated by alkaline hydrolysis into a neutral fraction, mostly unchanged hydrocarbon (IV), and a homogeneous acid fraction. In the latter a structure of type (VI) must be involved for (*a*) dehydrogenation gave no evidence of formation of derivatives of (II) and (*b*) ultra-violet absorption spectra were in accord with a diphenyl formulation (Fig. 2). Structures (VI*a* and *b*) were differentiated by a combination of infra-red spectroscopy and oxidative degradation.

The structure (VI*a*) for the analogous product from phenanthrene was proved by Drake and Sweeney by oxidative degradation to a *cyclo*propane derivative. If the presence of a fluorene rather than a diphenyl structure had no effect on the stability of a *cyclo*propane

ring it follows that oxidation of a structure such as (VI*a*) would lead to a product retaining the *cyclo*propane ring. Our product from the analogue (IV) was, however, readily oxidised to fluorenone-4 : 5-dicarboxylic acid, and so must have the *cyclo*heptatriene structure (VI*b*), and this was confirmed by infra-red spectroscopy.



(VI*a*) (VI*b*) (VII*a*) (VII*b*)

Repetition of the work of Drake and Sweeney and of Cook, Dickson, and Loudon with phenanthrene gave however results different from theirs. Cook, Dickson, and Loudon describe a methyl ester of m. p. 145° and both groups of workers found that the parent acid has m. p. 258°. In contrast, our methyl ester had m. p. 210° and our acid m. p. 248°.

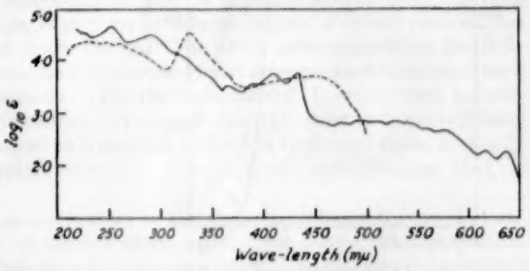


FIG. 1. *Absorption spectrum of* cyclo*hepta*[bc]*acenaphthylene,* —— *in hexane,* – – – – *in* 8N-HCl.

Both m. p.s were depressed on admixture with samples supplied by Dr. Loudon, so isomorphism is eliminated. The ultra-violet spectra (Fig. 2 and Table 1) showed that none the less the compounds were closely related.

TABLE 1. *Ultra-violet spectra* (*max. in* mμ).

Compound	M. p.	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	$\lambda_{max.}$
Me ester *	145°	308	3·72	296	3·68	270	4·14	—	—
Me ester †	210	306	3·66	296	3·66	270	4·14	—	—
Acid *	258	314	—	304	—	276	(infl.)	272	266
Acid †	248	308	—	295	(infl.)	276	(infl.)	272	267

* Previous work. † Present work.

Dr. Whiteley has examined, in the infra-red region, the acids, methyl esters, and reduction product of the acids with lithium aluminium hydride, which we obtained from the products (VI) and (VII) of interaction of *cyclo*penta[*def*]phenanthrene (IV) and phenanthrene with diazoacetic ester. A fundamental difference exists in the carbonyl absorption region for the acids and esters. These values (Table 2) should be compared

TABLE 2. *Infra-red spectra in* KBr *discs* (cm.$^{-1}$).

Acid (VI*b*)	1671	Ester (VI*b*)	1699
Acid (VII)	1722	Ester (VII)	1718

with 1715 and 1740 cm.$^{-1}$ which would be regarded as of the right order for aliphatic acids and esters. A marked conjugation effect is shown by the *cyclo*pentano-compounds (VI) but not by the phenanthrene derivatives (VII), thus indicating structure (VI*b*) for the former. Further, in the three products related to (VII) a band was found at 1004 cm.$^{-1}$ where it is known that many *cyclo*propane derivatives absorb. The three compounds derived from the *cyclo*pentaphenanthrene had no band in this region but the acid and ester had a band at 843 and 847 cm.$^{-1}$ respectively, which is the appropriate region for the C–H bonding vibration of a system $R_2C{:}CHR$; this band was missing in the reduction

product. Structure (VI*b*) is therefore extremely likely and in agreement with the ultraviolet evidence there is a close structural relation between the product of Drake and Sweeney, and of Cook, Dickson, and Loudon, and that described by us. Further work (to be reported later) will indicate that the difference is steric (cf. VII*a* and *b*).

The stability of the dihydro-ester derivative of (III) to dehydrogenation indicates the

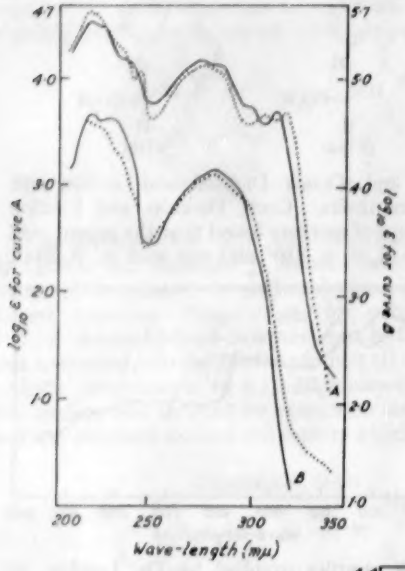


FIG. 2. *Absorption spectra* (*A*) *of* (——) *the acid, m. p.* 248°, *from phenanthrene and* (. . . . . .) *the product of its reduction with* $LiAlH_4$, *and* (*B*) (——) *the acid corresponding to the ester* (VI*b*) *and* (. . . . . .) *its reduction product with* $LiAlH_4$.

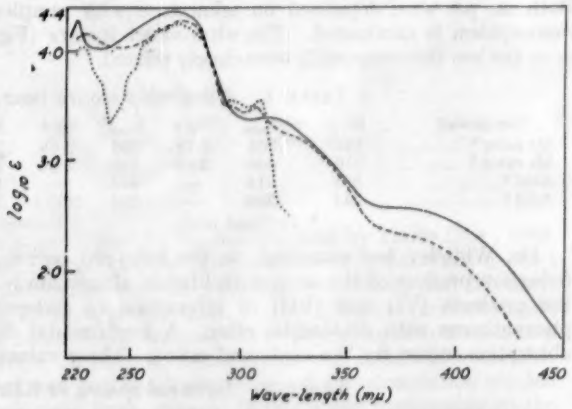


FIG. 3. *Absorption spectra of* (——) *fluorenone-4 : 5-dicarboxylic acid* (IX), (– – – –) *its dimethyl ester, and the diol* (VIII) *in* EtOH.

energetic disfavour of a structure such as (III). The absorption spectrum of the hydrocarbon (II) (Fig. 1) conforms to a pattern common to the azulenes and many anhydro-salts (unpublished work). The absorption of acid solutions of the compound (II) resembles that in neutral solvents in general form, with a bathochromic shift. The only markedly new feature is that the parent has extensive absorption in the visible region; this is found in most compounds requiring a " betaine "-type formulation and it is this band which is often abnormally affected by substitution and most dependent on the polar character of the environment.

The basicity of the azulene (II), measured in the normal manner (Plattner, Heilbronner, and Weber, *Helv. Chim. Acta*, 1949, **32**, 574), is contrasted in Table 3 with those of azulene,

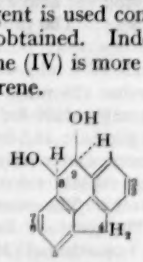
1 : 2-benzazulene and 5 : 6-benzazulene (W. Keller, Thesis, Eidg. Techn. Hochschule, Zurich, 1952). The values are expressed as the concentration of sulphuric acid which reduces by one-half the concentration of azulene present in an equal volume of toluene or *cyclo*hexane. The basicity of a hydrocarbon reflects the equilibrium, $Az + H^+ \rightleftharpoons AzH^+$

TABLE 3. *Basicity of polycyclic azulenes.*

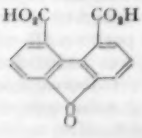
	H_2SO_4 (%)		H_2SO_4 (%)
Compound (II)	44·2	5 : 6-Benzazulene	61·7
1 : 2-Benzazulene	53·6	Azulene	51·0

(where Az = azulene). The forward reaction is favoured by a high polarisation of the ground state, and the reverse reaction is disfavoured by the stability of the resulting cation. In azulene and 5 : 6-benzazulene there are two positions which can act as proton acceptors : they are therefore comparable compounds. The large differences in basicity must arise from the influence of the condensed benzene ring on the initial degree of polarisation and/or the stability of the resulting cation. Both factors probably operate in the same direction, for in terms of resonance theory the more stable the cation type the higher the contribution of betaine forms, *i.e.*, the higher the degree of initial polarisation. Similarly, the compound (II) and 1 : 2-benzazulene have each one site for the addition of a proton; the high basicity of the compound (II) indicates that there is a large degree of initial polarisation and that the derived cation is much more stable. The close envelopment of the five-membered ring has thus enhanced, in this case, the azulenic character because it has increased the polarisation existing within the molecule. For the compound (III), where such polarisation is limited and where *cyclo*polyolefinic structures are the principal contributing structures, difficulty has been experienced in a synthesis which is typical of those normally employed for azulenes. It is therefore not the *cyclo*polyolefin contribution that is fundamental to azulene structure.

The results on the addition of diazoacetic ester to the *cyclo*pentaphenanthrene (IV) are of interest because it constitutes one of the few cases, apart from pyrene (Badger, Cook, and Gibb, *J.*, 1951, **3456**), where multiple attack occurs in a polycyclic compound containing one bond of outstandingly high double-bond character. The question therefore arises as to the effect of the five-membered ring on phenanthrene. With the more selective osmium tetroxide oxidation (Cook and Schoental, *J.*, 1948, 170) no evidence of attack other than on the 8 : 9-bond was found. The resulting glycol (VIII) was oxidised readily to fluorenone-4 : 5-dicarboxylic acid (IX). As the latter was a key compound in all of this work it was obtained by Kruber's method (*Ber.*, 1934, **67**, 1000) and the absorption spectrum of both the acid and its dimethyl ester were determined [Fig. 3, where the spectrum of the glycol (VIII) is also recorded]. The indication is, therefore, that little reliance should be placed on the use of diazoacetic ester for the determination of bond order unless a more specific reagent is used comparatively and proof of homogeneity of product and of its structure are obtained. Indeed the mixture obtained in this reaction with *cyclo*penta[*def*]phenanthrene (IV) is more closely allied to the mixtures obtained by electrophilic attack on phenanthrene.



(VIII)



(IX)

The spectra recorded for diphenyl derivatives, apart from that of (VIII), are in accord with those for 9 : 10-dihydrophenanthrene, fluorene, and 8 : 9-dihydro*cyclo*penta[*def*]phenanthrene (Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2130). The last compound differs from the first two in one respect. The fine side maxima (*ca.* 310 mμ) on the principal diphenyl absorption (*ca.* 270 mμ) are absent when two bridges join the 2 : 2′-positions of the diphenyl nucleus. Only in the glycol (VIII) are two such bridges found and also these side maxima. The presence of the cinnamic acid type side chain in (VI*b*) has apparently little influence

on the ultra-violet absorption, apart from a broadening of the absorption in the 220—230 mμ region. It is noticeable that after lithium aluminium hydride reduction this broadening disappears and the curve agrees closely with the others.

Experimental

M. p.s were determined on a Kofler block. Absorption spectra were determined with a Unicam S.P. 500 instrument.

γ-1-Acenaphthenylbutyric Acid.—Method I. Lithium aluminium hydride (5·475 g.) in ether (150 ml.) was added to a suspension of α-1-acenaphthenylacetic acid (21·2 g.) (Bachmann and Sheehan, *J. Amer. Chem. Soc.*, 1941, **63**, 204) at such a rate that the solution remained at the b. p. The mixture was set aside for 0·5 hr., then poured on ice in 4N-sulphuric acid (150 ml.). After 1 hr. the ether layer was separated and the aqueous phase was further extracted with ether and with benzene. The combined extracts were washed with water, dilute sodium hydroxide (2 × 100 ml.), and again water and dried (Na_2SO_4). Removal of the solvent and distillation (b. p. 149—151°/0·2 mm.) gave 2-1′-*acenaphthenylethanol* as a pale yellow, viscous oil (14·02 g., 70·7%) (Found : C, 84·6; H, 8·0. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%).

Phosphorus tribromide (5·4 g.) in ether (20 ml.) was added to 2-1′-acenaphthenylethanol (30·4 g.) in ice-cold ether (200 ml.). The mixture was allowed to come to room temperature (1 hr.). The excess of tribromide was decomposed with water (500 ml.), and the separated ether layer was washed with water, sodium hydrogen carbonate solution, and water. The dried (Na_2SO_4) extract was concentrated under reduced pressure. Drying was completed by azeotropic distillation with benzene, and the residual oily bromide (28·5 g.) was used without further purification.

The crude bromide (28·5 g.) in benzene (100 ml.) was added to diethyl malonate (35 ml.) in absolute ethanol (300 ml.) in which sodium (5·9 g.) had previously been dissolved. The mixture was kept for 3 days in a refrigerator, then boiled under reflux for 3 hr. The solvent was removed under reduced pressure and the resulting ester hydrolysed by boiling 40% potassium hydroxide solution (125 ml.) for 1 hr. The solution was cooled and extracted with ether to remove alkali-insoluble material. The malonic acid was then precipitated with concentrated hydrochloric acid. Inorganic material was removed by washing with ice-cold water, and the crude acid was then dried over P_2O_5 under reduced pressure. The yield (19·9 g., 45·7%) was poor owing to formation of a water-soluble phosphorus-containing side-product. The crude acid had m. p. 160—165°, raised by recrystallisation from water to 163—164° (gas evolution). Difficulty was experienced in obtaining satisfactory analyses for this compound as it appears to retain water (Found : C, 70·7; H, 5·3. Calc. for $C_{17}H_{16}O_4$: C, 71·8; H, 5·7%).

2-1′-Acenaphthenylethylmalonic acid (9·36 g.) was heated for 25 min. at 175—180°, liberation of carbon dioxide then being complete. The product was dissolved in excess of dilute sodium hydroxide solution, and insoluble material was removed by extraction with ether followed by benzene. γ-1-Acenaphthenylbutyric acid was extracted into ether after acidification. The dried (Na_2SO_4) extract was distilled, leaving the acid as an oil which crystallised as pale-buff needles after several hours (yield, 6·23 g., 79%). The product was identical with that from Method II.

Method II. Pure, freshly distilled thionyl chloride (6·7 ml.) was added to a suspension of β-1-acenaphthenylpropionic acid (16·15 g.) in dry ether (75 ml.). A little pyridine (4 drops) was then added and the mixture was kept at room temperature for 2 hr.; dissolution was then complete. The solvent was removed under reduced pressure and excess of thionyl chloride was distilled off with successive portions (15 ml.) of benzene under reduced pressure. The residue, dissolved in ether (75 ml.), was added dropwise to a rapidly stirred solution of diazomethane (from 40 g. of *N*-methyl-*N*-nitrosourea) in ether (400 ml.). The ether and excess of diazomethane were removed after 1 hr. at room temperature. The residual diazo-ketone was dissolved in methanol (75 ml.) and added to silver oxide (0·75 g.) in methanol (30 ml.) which had been boiled together under reflux until a silver mirror had been formed. Liberation of nitrogen began immediately but the mixture was boiled for 30 min. Further silver oxide (1·5 g. after 30 min., 0·75 g. after 4 hr.) was added and boiling continued for a total of 8—9 hr. (until a test with concentrated hydrochloric acid for diazo-ketone was negative). The silver oxide was removed and the resulting pale yellow solution boiled with charcoal for 10 min. and filtered through Filter-cel. Sodium hydroxide solution (15 ml.; 40%) was added and the solution was boiled for 1 hr. Most of the methanol was removed under reduced pressure and the residue was taken up in water (200 ml.). Insoluble and tarry material was extracted with ether and benzene.

Acidification of the aqueous phase yielded the acid as an oil which was extracted into ether (300 ml.). This was washed with water to remove mineral acid and after drying (Na_2SO_4) and removal of the solvent the *acid* was obtained as an oil (13·4 g., 78%) which crystallised overnight. It was obtained analytically pure by distillation in a tube [b. p. (tube) 170°/0·05 mm.]. Crystallisation of the distillate from light petroleum (b. p. 40—60°)–ether (5 : 1) gave colourless needles, m. p. 71—73° (Found : C, 79·8; H, 6·9. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%).

6 : 7 : 8 : 9-*Tetrahydro*-6-*oxo*cyclo*hepta*[bc]*acenaphthene*.—Phosphoric oxide was dissolved in 90% phosphoric acid to give a mixture of definite pentoxide content, by heating the mixture in a boiling-water bath with frequent swirling. The acid was added in one portion and, on continuation of the heating, dissolved to a deep orange solution. Swirling is necessary to ensure initimate contact. The reaction is best terminated by pouring the mixture into cold water after a preliminary cooling and should be done as soon as a dark scum begins to form on the surface of the phosphoric acid. The product was exhaustively extracted into ether, and washed with water and alkali to remove unchanged acid (which was recovered), and the ether layer was dried (Na_2SO_4) and distilled, to give the substiantially pure *ketone*, m. p. 109—111°; purification by crystallisation from acetone–ether (1 : 2) followed by two sublimations at 125°/0·05 mm. yielded colourless prisms, m. p. 110—111° (with sublimation) (Found : C, 86·0; H, 6·2. $C_{16}H_{14}O$ requires C, 86·4; H, 6·4%). The *dinitrophenylhydrazone* formed red prisms, m. p. 243° (Found : N, 13·8. $C_{22}H_{18}O_4N_4$ requires N, 13·9%). Some comparative experiments are tabulated.

Acid (g.)	Wt. of P_2O_5 / Wt. of acid	P_2O_5 (%) in acid	Time (min.)	Temp.	Yield (%)	Unchanged (%)
4·84	20 : 1	83	75	75°	38·2	46·3
10·26	25 : 1	78	140	100	57·1	—
9·63	30 : 1	78	45	100	82·6	Trace
9·27	30 : 1	78	40	100	86·3	Trace

6 : 7 : 8 : 9-*Tetrahydro*-6-*hydroxy*cyclo*hepta*[bc]*acenaphthene*.—A solution of the ketone (6·66 g.) in ether (90 ml.) and benzene (60 ml.) was added to lithium aluminium anhydride (0·75 g.) in ether (25 ml.) at such a rate as to maintain vigorous boiling. Boiling was continued for 1 hr. and the mixture poured into a cold saturated solution of ammonium chloride. After 1 hr. dilute sulphuric acid was added to complete the decomposition. The organic phase was separated and further extraction with ether (2 × 300 ml.) ensured complete separation of the alcohol. The extract was dried (Na_2SO_4) and the solvent was removed under reduced pressure, yielding the *alcohol* (6·70 g.) as colourless crystals, m. p. 140—143°. A sample crystallised successively from acetone, alcohol, and again from acetone melted at 144—145° (Found : C, 85·6; H, 7·1. $C_{16}H_{16}O$ requires C, 85·7; H, 7·2%).

8 : 9-*Dihydro*cyclo*hepta*[bc]*acenaphthene*.—The alcohol (4·50 g.) was dehydrated by phosphoric oxide (4·50 g.) in benzene (60 ml.). The solution became warm and was set aside for 30 min. without external heating. A further quantity of phosphoric oxide (3 g.) was added and the mixture was shaken for 2 hr., then poured into water and extracted with ether. The ether extracts were washed with water, sodium hydrogen carbonate solution, and water before being dried (Na_2SO_4). On removal of the solvent an oil (3·96 g.) was obtained which crystallised. Sublimation at 90°/0·05 mm. gave white crystals contaminated with a little red material. Recrystallisation from light petroleum (b. p. 40—60°) after passage through a short column of alumina gave the *hydrocarbon* as colourless platelets, m. p. 77—79° (Found : C, 93·1; H, 7·1. $C_{16}H_{14}$ requires C, 93·2; H, 6·8%). The *trinitrobenzene* complex had m. p. 135—137° (Found : C, 62·9; H, 4·1; N, 9·8. $C_{16}H_{14}.C_6H_3O_6N_3$ requires C, 63·0; H, 4·1; N, 10·0%).

6 : 7 : 8 : 9-*Tetrahydro*cyclo*hepta*[bc]*acenaphthene*.—This was prepared by Clemmensen reduction of the ketone in toluene with hydrochloric acid and amalgamated zinc. The toluene solution, after the reaction was complete, was separated and dried (Na_2SO_4) and evaporated, and the residue was sublimed at 80—85°/0·05 mm. and recrystallised from methanol containing a little light petroleum. The hydrocarbon crystallised as white needles melting over the range 45—67°. Analysis indicated that the material was substantially the desired hydrocarbon.

cyclo*Hepta*[bc]*acenaphthylene*.—The foregoing hydrocarbon (3·0 g.) and 20% palladium–charcoal (0·6 g.) were heated under nitrogen rapidly to 260° (oil-bath). The temperature was kept steady for 4 min. and then raised during 1·5 min. to 300° where it was maintained for 3 min. Liberation of hydrogen began at >220° and had just ceased at the end of the heating. The dark product was taken up in benzene and filtered through a short alumina column; elution was completed with 100 ml. of benzene–light petroleum (1 : 1). The combined red eluates were extracted with syrupy phosphoric acid (3 × 100 ml.). The acid extract was washed with

benzene before dilution with water (2 l.). The azulene was extracted with ether and the deep red extract was freed from acid by washing with water and sodium hydrogen carbonate solution before drying (Na_2SO_4) and concentration. The residue tended to pass from an oil to a solid but purification was completed by controlled elution with benzene–light petroleum (1 : 10) after adsorption from petroleum solution on alumina. The red material was thus separated from a brown strongly adsorbed impurity. The *hydrocarbon* crystallised readily as dark red leaflets, m. p. 142·5—143·5° (120 mg.), from light petroleum–benzene (Found : C, 94·9; H, 4·9. $C_{16}H_{10}$ requires C, 95·0; H, 5·0%). The *trinitrobenzene complex* formed orange-brown needles, m. p. 228—230° (Found : C, 64·0; H, 3·4; N, 10·0. $C_{16}H_{10},C_6H_3O_6N_3$ requires C, 63·6; H, 3·2; N, 10·1%).

cyclo*Hepta*[bc]*acenaphthylene and* 4 : 8-*Dihydro*cyclo*hepta*[def]*fluorene*-9-*carboxylic Acid from* cyclo*Penta*[def]*phenanthrene*.—The reaction between *cyclo*penta[*def*]phenanthrene (supplied by O. Kruber) and diazoacetic ester (Grundmann and Ottmann, *Annalen*, 1953, **582**, 163) was carried out in a 50-ml. pear-shaped flask, heated in an oil-bath and supplied with a small capillary dropping funnel, a nitrogen inlet tube, and an air-condenser drawn to a wide capillary at the exit end. The hydrocarbon (10 g.) was fused by raising the bath to 140° and this temperature was maintained while the diazoacetic ester (6·5 g.) was added dropwise during 2 hr. The mixture was stirred at this stage by a stream of nitrogen, and became reddish-brown. The temperature of the bath was finally raised during 5 hr. to 200° with only occasional stirring with the nitrogen stream. The reaction mixture was dissolved in benzene–light petroleum (3 : 1), and azulenic material was extracted into syrupy phosphoric acid (4 × 50 ml.). The acid layer was washed with further quantities of the same hydrocarbon mixture and was poured into water (2 l.). Extraction with ether gave the azulenic fraction. The solvent was removed from the dried extract (Na_2SO_4) to give a residue (4—5 g. in different experiments). When chromatographed on alumina (neutral) this gave two main bands. Elution with benzene gave the starting hydrocarbon (1·2 g.) which passes to some extent through the acid separation. Elution with benzene–ether (1 : 3) gave a band yielding a red azulenic oil (2 g.). A strongly adsorbed material, a brown oil (0·5 g.) eluted with acetone, accounted for the total amount chromatographed.

Chromatography of the red oil with slow elution by light petroleum–benzene gave two bands appearing green on the column but giving red eluates. The first yielded a red oil (1·4 g.) which tended to crystallise as needles but could not be obtained pure. The second gave an oil (0·6 g.) which showed no tendency to solidify. The two fractions were separately boiled for 2·5 hr. with 3% ethanolic potassium hydroxide (50 and 30 ml. respectively). The acids were obtained by pouring the mixtures into water, extraction of neutral material with benzene, acidification, and extraction with ether, and were amorphous solids (1 g. and 0·5 g. respectively). Decarboxylation in quinoline (20 ml. per g.) containing copper bronze (0·5 g. per g.) for 1 hr. at the b. p., cooling, extraction with ether, removal of quinoline by repeated extraction with dilute hydrochloric acid, washing with water, sodium hydrogen carbonate solution, and water, drying, and evaporation gave residues which on alumina each yielded one band which was eluted with light petroleum. The eluates yielded 150 and 30 mg., respectively, of the same crystalline hydrocarbon which formed from light petroleum deep red plates, m. p. 143·5—144·5°, identical (mixed m. p.) with *cyclo*hepta[*bc*]acenaphthylene. The trinitrobenzene complex, m. p. 228—230°, did not depress the m. p. of the derivative prepared from authentic material.

The brown oil eluted from the original column was subjected to the same procedure and gave a few mg. of the trinitrobenzene complex as above.

The material which was not extracted into phosphoric acid was examined. The original phase from the acid extract was washed with water and sodium hydrogen carbonate solution and dried (Na_2SO_4) and the solvent was removed by distillation. The residue was boiled for 3 hr. in ethanolic 3% potassium hydroxide (100 ml.). Most of the ethanol was removed by distillation under reduced pressure and the residue was taken up in water. Insoluble material was extracted into benzene and was worked up for starting hydrocarbon. The aqueous phase was acidified and the precipitated solid was found to be contaminated with a considerable amount of red material. The solid was taken up in benzene and again extracted with phosphoric acid. The phosphoric extract was diluted and the azulenic material re-extracted was decarboxylated, giving further quantites of the red azulene described above. The benzene solution containing material insoluble in phosphoric acid was washed and dried as before, and the residue after removal of the solvent was recrystallised repeatedly from ethanol. The product, 4 : 8-*dihydro*-cyclo*hepta*[def]*fluorene*-9-*carboxylic acid*, was isolated as colourless needles (720 mg. of pure material), m. p. 258° (Found : C, 82·0; H, 4·7. $C_{17}H_{12}O_2$ requires C, 82·2; H, 4·9%).

The *methyl ester* (105 mg.), obtained from the acid (100 mg.) with methanolic 3% hydrochloric acid, crystallised from benzene–light petroleum as colourless needles, m. p. 139—140°. Esterification with diazomethane gave the same product (Found : C, 82·9; H, 5·5. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%). The *ethyl ester*, prepared similarly, formed colourless needles, m. p. 141·5° (Found : C, 82·3; H, 5·9. $C_{19}H_{16}O_2$ requires C, 82·6; H, 5·8%).

4 : 8-*Dihydro*-9-*hydroxymethylene*cyclo*hepta*[def]*fluorene*.—The foregoing acid (190 mg.) was reduced with lithium aluminium hydride (50 mg.) in ether (25 ml.). The ether layer after decomposition of the complex with dilute sulphuric acid was washed with sodium hydrogen carbonate to remove acid. Removal of the ether, after drying (Na_2SO_4), gave the *alcohol* (180 mg.) which crystallised from benzene–light petroleum as colourless needles, m. p. 143° (Found : C, 87·0, 87·1; H, 5·6, 6·1. $C_{17}H_{14}O$ requires C, 87·1; H, 6·0%). In concentrated sulphuric acid it gave a blue-black colour.

Fluorenone-4 : 5-*dicarboxylic Acid*.—The acid (700 mg.) prepared as above was boiled for 12 hr. in " AnalaR " acetic acid (60 ml.) containing " AnalaR " chromic oxide (4·5 g.). The mixture was then poured into water and was extracted exhaustively with ether. The yellow ether extract was washed with water, and the acidic material was extracted from it with sodium hydrogen carbonate solution, giving a yellow salt in solution. The aqueous extract was acidified with hydrochloric acid and the precipitated acid was recrystallised three times from acetone–benzene. It yielded yellow prisms (125 mg.), m. p. 285—287° (Kruber, *loc. cit.*, gave m. p. 285°). The methyl ester, prepared by diazomethane (large excess), crystallised from light petroleum–benzene, as yellow needles, m. p. 191° (Found : C, 69·0; H, 4·2. Calc. for $C_{17}H_{12}O_5$: C, 68·9; H, 4·1%). The m. p.s of the acid and ester were not depressed on admixture with samples prepared by Kruber's method.

4b : 5a-*Dihydro*-5H-cyclo*propa*[def]*phenanthrene*-5-*carboxylic Acid*.—Phenanthrene (25 g.) was treated with diazoacetic ester (6 g.) under Drake and Sweeney's conditions (*J. Org. Chem.*, 1946, **11**, 67) and the ester resulting was separated from hydrocarbons by hydrolysis with ethanolic potassium hydroxide as described above. The alkali-soluble material was isolated by acidification and converted into the methyl ester by reaction with diazomethane followed by chromatography on alumina. The pure *ester* crystallised from light petroleum–benzene as colourless needles, m. p. 210° (Found : C, 81·4; H, 5·7. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%).

This was reduced with lithium aluminium hydride to an *alcohol*, forming colourless needles, m. p. 148° (Found : C, 86·1; H, 6·1. $C_{16}H_{14}O$ requires C, 86·4; H, 6·4%).

The ester (120 mg.) was hydrolysed with potassium hydroxide to give a quantitative yield of acid, m. p. 247—248° (from methanol), not raised by further crystallisation from methanol or benzene.

cis-8 : 9-*Dihydroxy*-8 : 9-*dihydroxy*cyclo*penta*[def]*phenanthrene*.—*cyclo*Penta[*def*]phenanthrene (410 mg.) was treated with osmium tetroxide (550 mg., 1 mol.) in dry thiophen-free benzene (15 ml.) containing pure pyridine (345 mg., 2 mols.). The mixture was left for 4 days during which crystals separated. After filtration the residue was washed with a little benzene, then taken up in methylene chloride, and after filtration the solvent was removed and the residue was weighed (1·20 g., 91%). The complex was redissolved in methylene dichloride and was shaken with an aqueous solution (100 ml.) of mannitol (10 g.) and potassium hydroxide (1 g.). The methylene chloride layer was separated and dried (Na_2SO_4). Removal of the solvent left a pale crystalline residue which was treated in boiling ethanol with charcoal for 10 min. Removal of the ethanol after filtration gave the yellow cis-*glycol* which after several recrystallisations from benzene formed colourless needles fusing to a yellow liquid at 180° (300 mg., 67% based on complex) (Found : C, 80·3; H, 5·5. $C_{18}H_{22}O_4$ requires C, 80·4; H, 5·4%).

This glycol (90 mg.) was boiled in glacial acetic acid containing chromic oxide (0·5 g.) for 2 hr. The acidic fraction of the product, crystallised three times from benzene–acetone, yielded yellow needles (15 mg.), m. p. 286° which did not depress the m. p. of fluorenone-4 : 5-dicarboxylic acid and had an identical absorption spectrum.

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Interaction of Polynitro-compounds with Aromatic Hydrocarbons and Bases. Part XV. The Association Constants for the Equilibria in the Systems: s-Trinitrobenzene–Benzene and Chloranil–Benzene.*

By J. M. Corkill, R. Foster, and D. Ll. Hammick.

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The competitive method described by Foster (*Nature*, 1954, **173**, 222) for the determination of equilibrium constants has been applied to the systems mentioned in the title. In each case, a series of *N*-alkylanilines was made to compete with the Lewis base benzene for the respective Lewis acids in *cyclo*hexane. Incidental to the work has been the evaluation of equilibrium constants for the equilibria between the *N*-alkylanilines and chloranil.

Colorimetric methods for the study of equilibria in solution of complex systems of the type $A + B \rightleftharpoons AB$, where AB is coloured, have the obvious advantage of directness compared with such a method as partition (Moore, Shepherd, and Goodall, *J.*, 1931, 1447; Anderson and Hammick, *J.*, 1950, 1089). However, in cases where A and B are coloured and where their absorption curves overlap to any extent with that of the product AB, calculations of equilibrium constants from optical data become complicated and tedious (cf., *e.g.*, Landauer and McConnell, *J. Amer. Chem. Soc.*, 1952, **74**, 1221; Lawrey and McConnell, *ibid.*, p. 6175). Moreover, since they involve differences between the total absorption and those of the separate components in the equilibrium, considerable inaccuracy may be inevitable. Thus, when determining the association constant of benzene–s-trinitrobenzene Lawrey and McConnell (*loc. cit.*) used solutions in which, at certain wave-lengths, benzene accounted for 90% of the total absorption.

A method has been suggested by one of us (Foster, *Nature*, 1954, **173**, 222) by which these difficulties can in certain circumstances be overcome. Suppose we wish to investigate the interaction of a substance A with a substance B′ by measuring the colour densities of the complex AB′, but find that the absorption of AB′ overlaps that of B′. We then seek an alternative substance to B′, say B″, having an absorption for the complex AB″ that does not overlap with that of any of the other species present. The equilibrium constant K'' for $A + B'' \rightleftharpoons AB''$ can easily be found by, say, the method of Foster, Hammick, and Wardley (*J.*, 1953, 3817). We can now add some B′ to the system $A + B'' \rightleftharpoons AB''$ and measure the diminution of the colour density of AB″ due to the shift of equilibrium in the system $A + B'' \rightleftharpoons AB''$ as a result of the interaction of B′ with some A, and hence arrive at the equilibrium constant K' for $A + B' \rightleftharpoons AB'$. This is essentially the principle of the Thomson and the Ostwald method for finding " acid strengths " by causing two acids to compete for a single base.

We can put this principle in an analytical form as follows: consider a solution containing a Lewis acid A and a pair of Lewis bases B′ and B″ which interact with A. For 1 : 1 interactions we have:

$$A + B' \rightleftharpoons AB'$$

$$A + B'' \rightleftharpoons AB''$$

A pair of equilibrium constants may be defined as:

$$K' = \frac{[AB']}{([\mathbf{A}] - [AB'] - [AB''])([\mathbf{B}'] - [AB'])}\ \dagger \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$K'' = \frac{[AB'']}{([\mathbf{A}] - [AB'] - [AB''])([\mathbf{B}''] - [AB''])} \quad . \quad . \quad . \quad . \quad (2)$$

where [AB′] and [AB″] are the equilibrium concentrations of AB′ and AB″. [**A**], [**B**′], and [**B**″] represent the total concentrations of these species respectively, namely, the sum of the

* Part XIV, *J.*, 1955, 89.

† Concentration terms which are determined analytically are printed in bold type.

amounts appearing in the free and in the "complexed" forms. If $[\mathbf{B}'] \gg [\mathbf{A}]$ and $[\mathbf{B}''] \gg [\mathbf{A}]$, then equations (1) and (2) become:

$$K' = \frac{[AB']}{[\mathbf{B}']([\mathbf{A}] - [AB'] - [AB''])} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$K'' = \frac{[AB'']}{[\mathbf{B}'']([\mathbf{A}] - [AB'] - [AB''])} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

from which:

$$[AB''] = \frac{K''[\mathbf{B}''][\mathbf{A}]}{K'[\mathbf{B}'] + K''[\mathbf{B}''] + 1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

For a wave-length at which the species A, B', B'', and AB' have negligible absorptions, but at which AB'' absorbs, let the extinction coefficient of AB'' be ε. If D_0 is the optical density at this wave-length for a solution containing A at a concentration $[\mathbf{A}]$, and B'' at a concentration $[\mathbf{B}'']$, but containing no B': also if D_1 is the optical density of a solution containing A and B'' at concentrations $[\mathbf{A}]$ and $[\mathbf{B}'']$, and B' at a concentration $[\mathbf{B}']$, then:

$$D_0 = \varepsilon \,.\, [AB'']_0, \qquad D_1 = \varepsilon \,.\, [AB'']_1$$

and

$$\frac{D_0}{D_1} = \frac{[AB'']_0}{[AB'']_1} = \frac{K'[\mathbf{B}'] + K''[\mathbf{B}''] + 1}{K''[\mathbf{B}''] + 1} \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

whence

$$K' = \frac{D_0 - D_1}{D_1}\left(\frac{(1 + [\mathbf{B}'']K'')}{[\mathbf{B}']}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Thus if K'' is known, a value of K' may be found.

Experimental.—To determine the association constants for the interactions of benzene with *s*-trinitrobenzene and with chloranil, alkylanilines were made to compete with the benzene for the respective Lewis acid, the charge-transfer band of the former fulfilling the conditions of equations (6) and (7).

The optical densities were measured in *cyclo*hexane at the wave-length corresponding to the maximum absorption in the charge-transfer bands of the respective Lewis acid–alkylaniline complexes, and are shown in the Tables (p. 1204). The instrument used in all the determinations was a Unicam SP 600 spectrophotometer, equipped with 4-cm. cells. Materials have been purified by methods described previously (Foster and Hammick, *J.*, 1954, 2685).

Discussion.—The degree of association of benzene with *s*-trinitrobenzene has been determined by Lawrey and McConnell (*loc. cit.*), using a direct photometric method. They give a value for an association constant defined as $k = [ab]/[a]$ (b), where [ab] is the equilibrium concentration of the complex, [a] is the equilibrium concentration of *s*-trinitrobenzene, and (b) is the mole fraction of benzene in equilibrium. Their value of $k = 4{\cdot}02 \pm 0{\cdot}02$ for benzene–*s*-trinitrobenzene in *n*-heptane corresponds to an association constant expressed in l./mole of $0{\cdot}60 \pm 0{\cdot}03$. This is in fair agreement with the value obtained in the present work, namely, $0{\cdot}77 \pm 0{\cdot}12$ l./mole. However, it is known that there is an increase of about 15% in the value of the association constant for *NN*-dimethylaniline–*s*-trinitrobenzene on changing the solvent from *n*-heptane to *cyclo*hexane (Foster and Hammick, *loc. cit.*). If the effect of this change of solvent is comparable in benzene–*s*-trinitrobenzene interaction, then a value of $0{\cdot}70 \pm 0{\cdot}04$ l./mole for the association of benzene–*s*-trinitrobenzene in *cyclo*hexane would be expected from the results of Lawrey and McConnell.

The association constant for chloranil and benzene is less than for *s*-trinitrobenzene–benzene. This is also true of the corresponding *N*-alkylaniline complexes (K'' in Tables 1

and 2). However, the maxima of the charge-transfer bands measured are at longer wave-lengths in the chloranil complexes with *N*-alkylanilines than in the respective *s*-trinitrobenzene complexes (λ in Tables 1 and 2).

TABLE 1. *The association constant for benzene–s-trinitrobenzene in* cyclo*hexane.* [**A**] = *ca.* 6 × 10^{-4}M. Temp. 19° ± 1°.

Competing base (anilines)	**B′** (M)	**B″** (M)	D_0	D_1	*K″* (l./mole) [1]	λ (mμ) [1]	*K′* (l./mole)
N-Methyl-	0·614	0·478	0·114	0·0990	7·8	435	0·96
,,	0·920	0·478	0·114	0·0948	7·8	435	0·90
,,	1·23	0·478	0·114	0·0940	7·8	435	0·72
NN-Dimethyl-	0·581	0·242	0·0752	0·0660	9·5	475	0·69
,,	1·02	0·242	0·0752	0·0610	9·5	475	0·76
,,	1·46	0·242	0·0752	0·0562	9·5	475	0·81
N-Ethyl-	0·615	0·447	0·107	0·100	8·4	445	0·54
,,	0·942	0·447	0·107	0·0958	8·4	445	0·60
,,	1·23	0·447	0·107	0·0912	8·4	445	0·67
NN-Diethyl-	0·615	0·148	0·116	0·0938	6·5	500	0·76
,,	0·942	0·148	0·116	0·0848	6·5	500	0·77
,,	1·23	0·148	0·116	0·0765	6·5	500	0·82
NN-Di-*n*-butyl-	0·291	0·0655	0·0472	0·0412	7·4	510	0·74
,,	0·437	0·0655	0·0472	0·0360	7·4	510	1·06
,,	0·727	0·0655	0·0472	0·0335	7·4	510	0·84

Mean: $K' = 0{\cdot}77 \pm 0{\cdot}13$ l./mole.

[1] Foster and Hammick, *J.*, 1954, 2685.

TABLE 2. *The association constant for benzene–chloranil in* cyclo*hexane.* [**A**] = *ca.* 6 × 10^{-4}M. Temp. 19° ± 1°.

Competing base (anilines)	**B′** (M)	**B″** (M)	D_0	D_1	*K″* (l./mole)	λ (mμ)	*K′* (l./mole)
N-Methyl-	0·390	0·209	0·0762	0·0687	5·0	590	0·56
,,	0·587	0·209	0·0762	0·0652	5·0	590	0·58
,,	0·782	0·209	0·0762	0·0625	5·0	590	0·57
NN-Dimethyl-	0·415	0·263	0·136	0·127	5·4	635	0·41
,,	0·623	0·263	0·136	0·120	5·4	635	0·52
,,	0·831	0·263	0·136	0·113	5·4	635	0·57
NN-Diethyl-	0·348	0·190	0·0317	0·0287	4·1	710	0·48
,,	0·695	0·190	0·0317	0·0260	4·1	710	0·56
,,	1·044	0·190	0·0317	0·0247	4·1	710	0·52
N-Butyl-	0·348	0·240	0·0212	0·0200	6·4	590	0·47
,,	0·590	0·240	0·0212	0·0185	6·4	590	0·64
,,	0·695	0·240	0·0212	0·0175	6·4	590	0·71
NN-Di-*n*-butyl-	0·347	0·223	0·0225	0·0205	3·8	720	0·52
,,	0·522	0·223	0·0225	0·0195	3·8	720	0·60
,,	0·695	0·223	0·0225	0·0185	3·8	720	0·58

Mean: $K' = 0{\cdot}56 \pm 0{\cdot}07$ l./mole.

Mulliken (*J. Amer. Chem. Soc.*, 1950, **72**, 605; 1952, **74**, 811; *J. Phys. Chem.*, 1952, **56**, 801) has expressed the ground state of charge-transfer complexes as:

$$\psi_N = a\psi(A,B) + b\psi(A^- - B^+) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where $\psi(A,B)$ is a "no-bond" function involving such terms as van der Waals, multi-pole, and London forces: $\psi(A^- - B^+)$ is a dative function in which the base molecule B has donated an electron to the acceptor molecule A. The corresponding excited state is:

$$\psi_E = a^*\psi(A^- - B^+) - b^*\psi(A,B) \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Excitation is the transition $\psi_N \longrightarrow \psi_E$.

The energies of the ground states of the complexes are small compared with the energies of excitation. Therefore the energies of the excited states must mainly account for the wave-length maxima of the charge-transfer bands. In equation (9) the coefficient a^* is very much greater than b^* (*idem, locc. cit.*). Thus it is the dative function which mainly

determines the energy of the excited state, and consequently the wave-length maximum of the charge-transfer band. The results suggest that this function is larger in chloranil than in the corresponding *s*-trinitrobenzene complexes (*i.e.*, chloranil is the stronger Lewis acid).

The association constant, on the other hand, is a measure of the function ψ_N. Because a is very much greater than b in equation (8) (*idem*, *locc. cit.*; Landauer and McConnell, *loc. cit.*) the lower values for the association constants of the chloranil complexes must presumably be due to the effect of the no-bond function.

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The Preparation and Properties of Some Dipyrazolyls.

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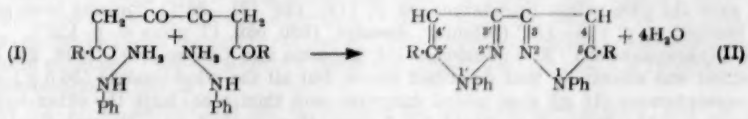
The preparations of **5 : 5′**-dimethyl-**1 : 1′**-diphenyl- and **1 : 1′ : 5 : 5′**-tetraphenyl-**3 : 3′**-dipyrazolyl have been repeated, and the **3 : 5′**-isomer of the latter has been isolated. Evidence is given for the orientations of these two isomers, and some **4 : 4′**-di-substituted derivatives of all three compounds have been prepared.

ACCORDING to Claisen and Roosen (*Annalen*, 1894, **278**, 294), two mols. of phenylhydrazine condense with one of octane-**2 : 4 : 5 : 7**-tetraone (I; R = Me) or **1 : 6**-diphenylhexane-**1 : 3 : 4 : 6**-tetraone (I; R = Ph) in glacial acetic acid to form respectively **5 : 5′**-dimethyl-**1 : 1′**-diphenyl- (II; R = Me) and **1 : 1′ : 5 : 5′**-tetraphenyl-**3 : 3′**-dipyrazolyl (II; R = Ph).

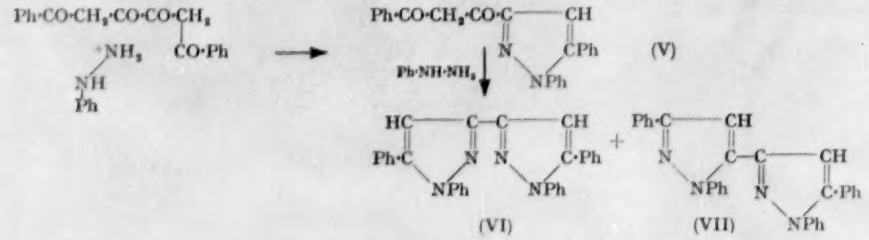


These orientations were assumed by analogy with the condensation of ethyl **2 : 4**-dioxopentanoate (III) and phenylhydrazine to form mainly ethyl 5-methyl-1-phenylpyrazole-3-carboxylate (IV) (Claisen, *ibid.*, p. 269). The condensations with the tetraketones have

been repeated, and the **3 : 3′**-dipyrazolyls isolated, but from **1 : 6**-diphenylhexane-**1 : 3 : 4 : 6**-tetraone, **1 : 1′ : 3′ : 5**-tetraphenyl-**3 : 5′**-dipyrazolyl (VII) was also isolated. The orientations of the isomers have been established as follows. From the reaction between phenylhydrazine (one mol.) and **1 : 6**-diphenylhexane-**1 : 3 : 4 : 6**-tetraone (one mol.) in acetic acid were obtained unchanged tetraketone, the **3 : 3′**-dipyrazolyl (II; R = Ph), and 3-α-benzoylacetyl-**1 : 5**-diphenylpyrazole (V). The ketone (V), on treatment with phenylhydrazine (one mol.) in acetic acid, gave two dipyrazolyls, one of which must be the **3 : 3′**- (VI), and the other the **3 : 5′**-isomer (VII). Infra-red absorption spectra measurements showed that Claisen and Roosen's dipyrazolyl is more symmetrical than the new compound; therefore the former is (VI) and the latter is (VII).

The isolation of the two isomers suggests that the reaction proceeds via (V) even when two mols. of phenylhydrazine are used, and is not as Claisen and Roosen (*loc. cit.*) suggested, a termolecular reaction.

In 1-phenylpyrazole standard reactions lead to 4-substituted derivatives (cf. Finar and Godfrey, *J.*, 1954, 2293), and so it has been assumed that the dipyrazolyls produce the corresponding 4 : 4′-disubstituted compounds. All three dipyrazolyls are readily converted into the corresponding 4 : 4′-dibromo-compounds, but when chloromethylated in acetic and (cf. Cambron, *Canad. J. Res.*, 1939, **17**, *B*, 10), only 1 : 1′ : 5 : 5′-tetraphenyl-3 : 3′-dipyrazolyl formed a 4 : 4′-bischloromethyl compound which could be isolated.



1 : 1′ : 5 : 5′-Tetraphenyl- and 5 : 5′-dimethyl-1 : 1′-diphenyl-3 : 3′-dipyrazolyl formed the corresponding 4 : 4′-bisacetoxymercuri-compounds by direct mercuration (cf. Paolini and Silbermann, *Gazzetta*, 1915, **45**, II, 385), and were orientated by conversion into the 4 : 4′-dibromo-compounds.

Experimental

Octane-2 : 4 : 5 : 7-*tetraone* (cf. Claisen and Stylos, *Ber.*, 1888, **21**, 1142; Freri, *Gazzetta*, 1938, **68**, 612).—To sodium methoxide [from methanol (16 g.) and sodium (12·5 g.)] under ether (300 c.c.) at 0° a mixture of dry ethyl oxalate (36·5 g.) and dry acetone (29 g.) was added with stirring during 25 min. The mixture was stirred for 2 days, then a solution of the solid in water (300 ml.) was acidified with acetic acid. After ½ hr. filtration and drying *in vacuo* ($CaCl_2$) gave the pale yellow tetraketone, m. p. 118—120° (21—38%), forming from methanol yellow needles, m. p. 120—121° (Schmidt, *Annalen*, 1950, **569**, 17, gives m. p. 123°).

1 : 6-*Diphenylhexane*-1 : 3 : 4 : 6-*tetraone* (cf. Brömme and Claisen, *Ber.*, 1888, **21**, 1131).—The method was essentially that described above, but all the ethyl oxalate (36·5 g.) and half of the acetophenone (15 g.) were added dropwise, and then 4 hr. later the other half of the acetophenone. The liquid was stirred for 3 days, then worked up. Recrystallisation from chloroform gave bright yellow needles, m. p. 177—179° (62—74%).

5 : 5′-*Dimethyl*-1 : 1′-*diphenyl*-3 : 3′-*dipyrazolyl* (cf. Claisen and Roosen, *Annalen*, 1894, **278**, 294).—Octane-2 : 4 : 5 : 7-tetraone (3·4 g., 0·02 mole) was heated with phenylhydrazine (4·3 g., 0·04 mole) in acetic acid (40 c.c.), on the steam-bath for 1 hr., cooled, and diluted with water, and the precipitate recrystallised from aqueous acetic acid (3·4 g.; 55%) as fine pale buff needles, m. p. 141—142°.

1 : 1′ : 5 : 5′-*Tetraphenyl*-3 : 3′- *and* 1 : 1′ : 3′ : 5-*Tetraphenyl*-3 : 5′-*dipyrazolyl* (*cf.* idem, loc. cit.).—1 : 6-Diphenylhexane-1 : 3 : 4 : 6-tetraone (47·2 g., 0·16 mole) was added to phenylhydrazine (34·6 g., 0·32 mole) in glacial acetic acid (250 c.c.), and the mixture heated on the steam-bath for 3—4 hr. The tetraketone dissolved within a few minutes, and then slowly a precipitate was formed. The mixture was cooled and filtered, and the precipitate washed with acetic acid and then with water, dried at 120°, and recrystallised from benzene (yield, 35·2 g., 49·5%). This was 1 : 1′ : 5 : 5′-tetraphenyl-3 : 3′-dipyrazolyl, m. p. 233° (Claisen and Roosen, *loc. cit.*, give m. p. 232°).

The filtrate was diluted with much water. The precipitated yellow wax was filtered off and dissolved in hot methanol (200 c.c.), and a few drops of water were added. After 3 days a small precipitate was filtered off and the filtrate was evaporated to 170 c.c. and left until a further precipitate was deposited. The filtrate was again reduced in bulk by evaporation, and the process repeated until no further precipitate was deposited. Occasionally a few drops of water had to be added to ensure precipitation; too much water caused an oil to be deposited. All the precipitates were combined, and repeated recrystallisation from methanol (charcoal) and then from light petroleum (b. p. 90—100°) gave 1 : 1′ : 3′ : 5-*tetraphenyl*-3 : 5′-*dipyrazolyl* (12·2 g., 17·3%) as fine white needles, m. p. 135—136° (Found: C, 81·8; H, 5·2; N, 12·7. $C_{30}H_{22}N_4$ requires C, 82·2; H, 5·0; N, 12·8%).

3-α-*Benzoylacetyl*-1 : 5-*diphenylpyrazole*.—To 1 : 6-diphenylhexane-1 : 3 : 4 : 6-tetraone (58·8 g., 0·2 mole) suspended in acetic acid (750 c.c.) on a steam-bath was added dropwise during 2·75 hr., a solution of phenylhydrazine (21·6 g., 0·2 mole) in acetic acid (250 c.c.). The mixture was heated for a further 1·25 hr., then set aside for 2 days. The precipitate (P) was filtered off. The filtrate was treated with much water and the precipitate (P5) dissolved in hot acetic acid (200 c.c.); cooling gave a precipitate (P6) (2·1 g.). The original precipitate (P) was washed with acetic acid, then with water, dried *in vacuo* ($CaCl_2$), and digested with benzene (2 × 250 c.c.), leaving a residue (R1) (3·1 g.). The benzene extract was evaporated and the residue refluxed with ethyl acetate (400 c.c.) and filtered hot, giving a residue (R2) (3·2 g.). Cooling this filtrate gave a precipitate (P1) (1·2 g.), and evaporation of the mother-liquors therefrom to 300 c.c. gave, after cooling, a precipitate (P2) (1·4 g.). The filtrate from P2, when kept overnight, gave further material (P3) (3·3 g.); removal of this, evaporation to 120 c.c., and cooling gave a solid (P4) (10·1 g.), and a liquor whence no further precipitate was obtained. The material R1 was unchanged tetraketone. Materials R3, P1, and P2 were 1 : 1′ : 5 : 5′-tetraphenyl-3 : 3′-dipyrazolyl. Material P3 and, after recrystallisation from aqueous acetic acid, materials P4 and P6 formed pale yellow needles, m. p. 164—166·5°, and were shown to be 3-α-*benzoylacetyl*-1 : 5-*diphenylpyrazole* (Found : C, 79·1; H, 4·9; N, 8·1. $C_{24}H_{18}O_2N_2$ requires C, 78·7; H, 4·9; N, 7·7%) by formation of a violet colour with ethanolic ferric chloride, a purple colour in Knorr's pyrazoline test, and, on oxidation with alkaline permanganate, 1 : 5-diphenylpyrazole-3-carboxylic acid, m. p. 185—186° (Claisen and Beyer, *Ber.*, 1887, **20**, 2186) alone or mixed with a specimen prepared as below.

Orientation of the Isomeric Tetraphenyldipyrazolyls.—3-α-Benzoylacetyl-1 : 5-diphenylpyrazole (2·9 g., 0·008 mole) and phenylhydrazine (0·97 g., 0·009 mole) in acetic acid (60 c.c.) were heated on the steam-bath for 1 hr., then kept overnight. The precipitate was filtered off and recrystallisation from benzene gave 1 : 1′ : 5 : 5′-tetraphenyl-3 : 3′-dipyrazolyl (2·4 g., 69%), m. p. 232—233°. Dilution of the acetic acid filtrate with water produced a precipitate which, after drying ***in vacuo*** over calcium chloride and recrystallisation from light petroleum (b. p. 90—100°), gave 1 : 1′ : 3′ : 5-tetraphenyl-3 : 5′-dipyrazolyl (1 g., 23%), m. p. 134·5—135·5°. The infra-red spectra, obtained from Nujol suspensions, were complex and similar, the main difference being that several absorption bands of Claisen and Roosen's dipyrazolyl are split into two bands for the new dipyrazolyl. In general, the lowering of the symmetry in the 3 : 5′-isomer increases the number of bands. In the region of the spectrum most influenced by changes in structure, 1600—650 cm.$^{-1}$, Claisen and Roosen's dipyrazolyl has 19 strong bands, and the new compound has 25.

I thank Mr. D. E. Bethell and Mr. G. Higgins for the spectroscopic data, and Dr. L. C. Bateman of the British Rubber Producers' Research Association for providing facilities for the spectroscopic work.

1 : 5-*Diphenylpyrazole*-3-*carboxylic Acid*.—Bischler (*Ber.*, 1892, **25**, 3143) prepared this acid by reaction between benzenediazonium chloride and ethyl phenacylacetoacetate (prepared ***in situ*** by Paal's method, *Ber.*, 1883, **16**, 2866). By this method we found it very difficult to obtain the acid crystalline. The following modification was more satisfactory (cf. Ossipoff and Korschun, *Chem. Zentr.*, 1903, **7**, II, 1281). To sodium wire (5·4 g., 0·235 g.-atom) under dry ether (400 c.c.) was added ethyl acetoacetate (30 g., 0·23 mole), and the mixture heated under reflux for 6 hr. To this mixture, when cool, was added an ethereal solution of phenacyl bromide (46 g., 0·23 mole) at a rate to maintain gentle reflux. Finally the mixture was refluxed for a further 2 hr. and then set aside overnight. The ethereal solution was washed repeatedly with water, then dried (Na_2SO_4), and the ether removed under reduced pressure. Ethyl phenacylacetoacetate was left as a red oil (56 g.). To this (12·4 g., 0·05 mole) in ethanol (200 c.c.) immersed in ice was added a cold solution of benzenediazonium chloride (4·65 g.), and then sodium acetate (16·4 g., 0·2 mole) in ice-cold water (40 c.c.; cf. Morgan and Reilly, *J.*, 1913, **103**, 808). The mixture was set aside for 24 hr. in ice, then diluted with water, and the oil that separated was heated on the steam-bath for 15 min. with sodium hydroxide (6 g.) in a small amount of water. The liquid, after cooling, was acidified with hydrochloric acid, and the precipitate, after repeated recrystallisation from methanol (charcoal) and then benzene, gave 1 : 5-diphenylpyrazole-3-carboxylic acid (6·7 g., 51%), m. p. 185—186°.

4 : 4′-*Dibromo-compounds*.—A chloroform solution of the dipyrazolyl was treated with bromine at room temperature, and the chloroform evaporated, and the residue recrystallised, giving : 4 : 4′-*dibromo*-5 : 5′-*dimethyl*-1 : 1′-*diphenyl*-3 : 3′-*dipyrazolyl* (from aqueous acetic acid), short cream-coloured rods, m. p. 159—160° (Found : Br, 33·9. $C_{20}H_{16}N_4Br_2$ requires Br, 33·9%); 4 : 4′-*dibromo*-1 : 1′ : 5 : 5′-*tetraphenyl*-3 : 3′-*dipyrazolyl* (from chloroform), pale cream-coloured

plates, m. p. 272—273° (Found: Br, 27·2. $C_{30}H_{20}N_4Br_2$ requires Br, 26·8%); **4 : 4′-*dibromo*-1 : 1′ : 3′ : 5-*tetraphenyl*-3 : 5′-*dipyrazolyl*** (from chloroform–ligroin), white rosettes, m. p. 200—201° (Found: Br, 27·1%).

4 : 4′-*Bischloromethyl*-1 : 1′ : 5 : 5′-*tetraphenyl*-3 : 3′-*dipyrazolyl*.—To a warm solution of the dipyrazolyl (13·2 g., 0·03 mole) in acetic acid (120 c.c.) and concentrated hydrochloric acid (26 c.c.) was added paraformaldehyde (2·4 g., 0·08 mole), and the mixture heated for 2 hr. on the steam-bath, then allowed to cool and filtered. The precipitate was washed with acetic acid and then with water, dried *in vacuo* ($CaCl_2$), and recrystallised from chloroform. This gave the ***bischloromethyl compound***, white needles (6·2 g., 39%), m. p. 274—276° (Found: C, 71·3; H, 4·5; N, 10·4; Cl, 13·3. $C_{32}H_{24}N_4Cl_2$ requires C, 71·8; H, 4·5; N, 10·5; Cl, 13·3%).

4 : 4′-*Bisacetoxymercuri*-5 : 5′-*dimethyl*-1 : 1′-*diphenyl*-3 : 3′-*dipyrazolyl*.—To the dipyrazolyl (3·14 g., 0·01 mole) in acetic acid (60 c.c.) was added recrystallised mercuric acetate (6·37 g., 0·02 mole), and the mixture heated on the steam-bath for 30 min. To the cool mixture was added water (200 c.c.), and the precipitate was filtered off, washed, and recrystallised from aqueous acetic acid. This gave the **4 : 4′-*bisacetoxymercuri-compound*** (4·8 g., 58%) as white needles, m. p. 204—204·5° (Found: Hg, 47·9. $C_{34}H_{32}O_4N_4Hg_2$ requires Hg, 48·3%).

4 : 4′-*Bisacetoxymercuri*-1 : 1′ : 5 : 5′-*tetraphenyl*-3 : 3′-*dipyrazolyl*.—To a suspension of the dipyrazolyl (4·38 g., 0·01 mole) in acetic acid (150 c.c.) was added recrystallised mercuric acetate (6·37 g., 0·02 mole), and the mixture refluxed for 5 hr. The liquid always contained solid; the dipyrazolyl appeared to dissolve and then to be reprecipitated as a white powder. The mixture was allowed to cool, and the solid filtered off and then digested with chloroform (4 × 25 c.c.), and dried. The **4 : 4′-*bisacetoxymercuri-compound*** (7·6 g., 69%) was a white powder, m. p. 271·5° (Found: Hg, 41·4. $C_{34}H_{26}O_4N_4Hg_2$ requires Hg, 42·0%).

The corresponding **4 : 4′-dibromo-compounds** were obtained from the mercuri-compounds by treatment in acetic acid with bromine at room temperature. When boiled with dilute hydrochloric acid, the mercuri-compound of the dimethyldipyrazolyl gave **5 : 5′-dimethyl-1 : 1′-diphenyl-3 : 3′-dipyrazolyl**. **1 : 1′ : 5 : 5′-Tetraphenyl-3 : 3′-dipyrazolyl**, however, could be obtained from its mercuri-compound only by refluxing the latter for some time with acetic acid containing concentrated hydrochloric acid.

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*The Conductivity of Silver Nitrate in Non-aqueous and Mixed Solvents. Part II.**

By V. S. GRIFFITHS and K. S. LAWRENCE.

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The variation of the conductivity of silver nitrate in 1 : 4-dioxan–water solutions, in acetone, and in acetone–water mixtures is reported and discussed.

THE effect of solvent composition on the conductivity of electrolytes has been studied frequently, the greatest attention having been paid to water-rich binary aqueous organic solvent solutions. James (*J.*, 1950, 1094; 1951, 153) showed that for certain electrolytes (*e.g.*, lanthanum ferricyanide and zinc and copper sulphates) in water-rich acetone, glycol, ethanol, and dioxan solutions the deviations from Onsager's theory (*Physikal. Z.*, 1927, **28**, 277) could reasonably be accounted for in terms of ion-association based upon Bjerrum's theory (*Kgl. Danske Videnskab. Selsk.*, 1926, **7**, No. 9) which supposes purely coulombic forces to exist between the constituent ions. However the data for zinc malonate could not be treated as satisfactorily on this basis and it was suggested that the association in this salt is not governed solely by coulombic forces. Support for this idea can be found in the behaviour of organic acids in mixed solvents, *e.g.*, the data of Harned and Done for formic acid in 20%-dioxan–water solutions (*J. Amer. Chem. Soc.*, 1941, **63**, 2579) give a dissociation constant 100 times as great as that calculated on the basis of simple electrostatic forces by use of a Bjerrum "*a*" parameter obtained for aqueous solutions.

Although many data are available for the variation of conductivity in organic solvents

* Part I, *J.*, 1954, 686.

which can be used to test Bjerrum's ion-association theory, organic-solvent rich water mixtures have not been as fully studied. Consequently it was decided to study the behaviour of silver nitrate in mixed solvents of the latter type and to apply to the results Bjerrum's theory in an attempt to determine whether or not forces other than simple electrostatic forces obtain in the ion-association process. The results are presented in the Table.

Conductivities of silver nitrate in the acetone–water system at 25°.

10^4C	Λ	10^4C	Λ	10^4C	Λ	10^4C	Λ
Dry acetone.				5%-Water.			
0·21997	56·38	8·8483	14·12	0·6316	119·4	12·22	50·15
0·39361	44·45	9·3171	13·74	0·6824	116·6	16·50	44·75
0·65037	35·94	11·147	13·29	1·082	107·5	22·02	40·07
1·1157	28·63	12·755	12·92	1·508	99·37	26·99	37·05
1·4260	25·92	13·981	12·70				
1·9440	22·89	14·949	12·48	10%-Water.			
2·6740	20·42	16·153	12·34	0·1042	120·9	1·251	110·8
4·1271	17·40	17·257	12·22	0·2205	120·2	1·455	110·0
5·3988	15·98	18·870	12·09	0·2429	119·0	1·821	107·6
6·1277	15·56	20·335	11·98	0·4859	117·9	2·059	105·7
7·6585	14·37	22·428	11·82	0·6941	116·2	3·045	101·0
7·7054	14·61			0·8214	114·5	4·591	94·40
				0·9321	114·0	7·491	85·91
1%-Water.				1·214	111·8	10·92	78·83
0·01418	155·4	0·9188	53·16				
0·02106	151·6	1·222	47·14	20%-Water.			
0·03577	143·4	1·402	43·74	0·6365	93·52	2·330	90·55
0·05588	132·4	1·713	40·80	0·6938	93·26	3·017	89·61
0·08413	120·3	2·131	36·88	0·8140	93·06	3·521	89·06
0·09233	116·6	2·547	34·50	0·9789	92·75	3·565	89·16
0·1377	104·7	2·825	32·81	1·229	92·37	5·010	87·49
0·3001	81·87	3·495	29·80	1·255	91·95	6·637	86·06
0·3699	73·98	4·359	27·64	1·601	91·52	9·640	83·49
0·4150	72·92	5·453	25·31	2·008	91·12	11·37	82·31
0·7017	59·39						
				40%-Water.			
2%-Water.				0·3015	78·51	2·594	76·83
0·03842	157·5	1·503	61·37	0·6882	78·15	2·968	76·73
0·06290	149·4	2·159	51·43	0·7686	77·95	3·499	76·45
0·08769	146·7	3·078	44·70	1·174	77·64	3·608	76·33
0·1409	128·8	4·642	37·87	1·327	77·53	4·210	76·16
0·2485	112·4	6·306	33·51	1·713	77·34	4·856	76·03
0·3548	101·8	7·913	30·63	1·970	77·16	5·380	75·61
0·5417	88·97	9·528	28·50	2·356	76·96	6·176	75·48
0·7688	78·80	11·79	26·29				
1·166	67·64			50%-Water.			
				0·6062	76·99	1·919	76·37
5%-Water.				0·8477	76·82	2·088	76·21
0·07440	142·8	2·105	91·00	1·058	76·67	2·347	76·21
0·1464	138·9	2·494	86·27	1·112	76·67	2·632	76·07
0·2387	133·9	3·356	79·32	1·326	76·55	2·933	75·91
0·3286	129·4	4·307	72·71	1·596	76·45	3·611	75·75
0·4646	123·9	7·920	58·85				

Conductivities of silver nitrate in the dioxan–water system.

10^4C	Λ	10^4C	Λ	10^4C	Λ	10^4C	Λ
10%-Water.				20%-Water.			
1·804	1·46	5·882	0·92	0·611	32·36	3·235	23·55
2·280	1·35	7·853	0·82	0·774	31·00	3·572	22·93
2·886	1·27	7·960	0·80	1·055	29·84	4·339	22·12
2·889	1·23	9·610	0·75	1·464	28·06	5·984	20·13
3·349	1·15	12·96	0·66	1·971	26·79	8·222	18·64
4·256	1·05	14·44	0·64	2·482	25·28	11·22	17·05
4·908	0·99	16·00	0·61				
5·408	0·96	19·65	0·55	30%-Water.			
		25·05	0·50	2·264	42·71	12·82	36·33
				4·402	40·80	13·95	35·71
				6·661	39·41	16·04	35·01
				8·409	38·40	17·32	34·63
				8·935	38·12	20·55	33·75
				11·35	36·98		

Acetone–water system.

Percentage of organic solvent	Λ_0	K	D	$\Lambda_0 . \eta$ *	a, Å
100	206	3×10^{-6}	19·1	0·63	1·5
99	185·18	$9·90 \times 10^{-6}$	19·6	0·60	1·62
98	185·77	$2·23 \times 10^{-5}$	20·1	0·62	1·68
95	154·49	$1·62 \times 10^{-4}$	21·6	0·57	1·85
90	124·45	$1·18 \times 10^{-3}$	24·0	0·54	2·02
80	95·83	$9·86 \times 10^{-3}$	29·6	0·59	2·36
60	79·05	$4·51 \times 10^{-2}$	41·8	0·83	2·06
50	77·72	$9·07 \times 10^{-2}$	48·2	0·96	1·91

Dioxan–water system.

90	25	5×10^{-7}	5·6	0·35	4·7
80	41·32	$1·54 \times 10^{-4}$	10·71	0·72	5·05
70	47·62	$2·96 \times 10^{-3}$	17·69	0·91	5·98
0 †	133·36	1·47	78·5	1·19	2·65

* η is the viscosity of the solvent. † From Davies and Robinson (*J.*, 1951, 574).

Discussion

From the experimental results shown values of Λ_0 and of K, the dissociation constant, were calculated by Shedlovsky's extrapolation method (*J. Franklin Inst.*, 1938, **225**, 739), by use of values of the extrapolation function tabulated by Daggett (*J. Amer. Chem. Soc.*, 1951, **73**, 4977). Many of the results were also treated by the extrapolation methods of Fuoss and Kraus (*ibid.*, 1933, **55**, 476) as modified by Fuoss (*ibid.*, 1935, **57**, 488) and Davies (*J.*, 1933, 645), giving values of Λ_0 and K very close to those obtained by the Shedlovsky extrapolation (see Harned and Owen "The Physical Chemistry of Electrolytic Solutions," 2nd Edn., 1949, Reinhold, New York, p. 190, 591; James, *J.*, 1951, 153). A representative set of results, those for silver nitrate in an aqueous dioxan solution containing 80% by weight of dioxan, is shown.

Method	Λ_0	10^4K	Method	Λ_0	10^4K
Fuoss and Kraus	41·30	1·79	Davies	41·61	1·73
Shedlovsky	41·32	1·54			

The extrapolation plots for aqueous dioxan and aqueous acetone solutions were linear up to Fuoss's critical concentration (*J. Amer. Chem. Soc.*, 1935, **57**, 2604) but those obtained for the acetone solutions were somewhat puzzling. Whichever method of extrapolation was used, very marked deviations from linearity occurred at concentrations very much smaller than the critical concentration, and indeed Λ_0 and K were obtained by the extrapolation of the linear portion of the curve to give a value of $\Lambda_0 = 206$, which compares favourably with the sum of the mobilities (208) given by Davies ("Conductivity of Solutions," 2nd Edn., Chapman and Hall, London, 1933, p. 207). It has been suggested tentatively that in such solutions triple-ion formation occurs [see Griffiths and Lawrence (*Research*, 1953, **6**, No. 11); cf. French and Roe (*Trans. Faraday Soc.*, 1953, **49**, 627)] and Kraus (*J. Phys. Chem.*, 1954, **58**, 673) has pointed out that as the dielectric constant decreases to a value in the neighbourhood of $D = 20$ triple-ions are formed, but as yet no satisfactory quantitative conclusion has been reached. It must be emphasised that the accuracy of the results obtained for both Λ_0 and K in acetone and in aqueous dioxan solutions containing 90% of dioxan is not of the highest order in view of the weakness of the electrolyte in these solvents (Kilpatrick, *J. Chem. Phys.*, 1940, **8**, 306).

Bjerrum's "a" parameter (*loc. cit.*) was calculated for all solutions, the value in aqueous dioxan varying between 4·7 and 6·0 Å suggesting that solvation molecules may be retained in the ion-association process (cf. Burgess and Kraus, *J. Amer. Chem. Soc.*, 1948, **70**, 706). In acetone and aqueous acetone solutions however the order of the "a" parameter was 2 Å, a value smaller than the sum of the ionic radii, which may be taken to indicate that there is greater interaction between the ions than would be expected if only electrostatic forces obtained. It must be remembered, however, that the macroscopic dielectric constant has been used in these calculations, whereas Hasted, Ritson, and

Collie (*J. Chem. Phys.*, **1948**, **16**, 1) have shown that in aqueous solutions at distances of less than 4 Å from an ion the dielectric constant is a rapidly varying quantity, and not too great a reliance should be placed upon these values (cf. Bell and George, *Trans. Faraday Soc.*, 1953, **49**, 619; Kraus *loc. cit.*). The $\Lambda_0\eta$ values in both systems show a considerable variation beyond a concentration of 10% of water, a fact that is often taken to indicate that solvation changes are occurring (James, *loc. cit.*), an idea which is not easy to reconcile with other features of this work. For instance, with these mixed solvents, in solutions containing even small quantities of water, the water molecules greatly outnumber the ions [Hughes and Hartley (*Phil. Mag.*, 1933, **15**, 610) show that in a 0·0001N-salt solution containing 0·25% of water the ratio of salt ions : water molecules : methanol molecules is 1 : 500 : 125,000] and since, on general grounds, solvation by water molecules would be a predominating process, it is to be expected that the first additions of water will have the major effect as far as solvation is concerned.

It is seen that as the water content of the solution increases, the value of K increases, *i.e.*, it appears that dissociation is increasing with increasing dielectric constant.

Moelwyn-Hughes (" The Kinetics of Reactions in Solution," 2nd Edn., 1947, p. 198) discusses the variation of K with dielectric constant in terms of the Wynne-Jones equation

$$\frac{\mathrm{d}(\ln K)}{\mathrm{d}(1/D)_{T,P}} = \frac{Z_A Z_B e^2}{r k T}$$

where r is the sum of the ionic radii, D the dielectric constant of the solvent, and $Z_A Z_B$ are the valencies of the ionic species.

In particular, solutions of silver nitrate in water, methanol, and ethanol were considered and it is shown that a plot of ΔG against $1/D$ gives a straight line from the slope of which an r value of 2·681 Å is calculated, compared with the sum of the ionic radii determined from ionic mobilities, 2·675 Å. This value would thus appear to be independent of solvent. If the matter be pursued further, it can be shown that the data for other solvents, *e.g.*, pyridine, ethylenediamine, acetonitrile, etc., plotted in this manner give points which are widely dispersed about the line joining the points for water, methanol, and ethanol. It is perhaps significant that the latter hydroxylic solvents are considered to be the levelling solvents whilst the former are the differentiating solvents (Davies, " Conductivity of Solutions," 2nd Edn., 1933, Chapman and Hall, p. 229, 231; Glasstone, " Electrochemistry of Solutions," 2nd Edn., 1937, Methuen, London, p. 176) where it would be unwise to suppose that the sum of the ionic radii is independent of solvent.

However, in the work described here it was felt that if the preferential solvation of the ions with water molecules occurs, then at least within any one system the plot of pK against $1/D$ should be linear. This was found to be so in the case of aqueous dioxan solutions, but the acetone–water system gave points which fitted a steep curve.

It thus appears that whilst dioxan–water systems give satisfactory results when treated with theories based on electrostatic forces between ions, the acetone–water systems present many problems. It is clear that silver nitrate in acetone is a much weaker electrolyte ($K = 4 \times 10^{-6}$) than would be expected in a solvent with a dielectric constant of about 20 [*e.g.*, ethanol, $D = 24$, $K = 4{\cdot}4 \times 10^{-3}$ (Copley, Murray-Rust, and Hartley, *J.*, 1930, 2492)]. The very marked curvature of the extrapolation plots (Griffiths and Lawrence, *Research*, 1953, **6**, No. 11) is of interest, since Reynolds and Kraus (*J. Amer. Chem. Soc.*, 1948, **70**, 1709) applied Fuoss and Kraus's method (*loc. cit.*) to the conductivity data for a variety of salts in acetone and obtained only very slight deviations from linearity, whilst several workers, *e.g.*, Corignan and Kraus (*J. Amer. Chem. Soc.*, 1949, **71**, 2983), Luder and Kraus (*ibid.*, 1947, **69**, 2481), Bromley and Luder (*ibid.*, 1944, **66**, 107), who used silver nitrate in basic solvents also obtained almost linear plots. It thus appears that the combination of silver nitrate and acetone leads to " abnormal " results, and an attempt has been made to explain them in terms of acid–base forces (Griffiths and Lawrence, *loc. cit.*). As the water content of the system increases the dissociation constant rises, and it is interesting to note that in 90%-acetone solutions where $D = 24{\cdot}0$, K is of the same order, *i.e.*, $1{\cdot}18 \times 10^{-3}$, as that holding in ethanol solutions, namely $4{\cdot}4 \times 10^{-3}$.

EXPERIMENTAL

Procedure.—Conductivity measurements were made at 25° ± 0·01° with the apparatus described by Davies (*J.*, 1937, **432**). A Sullivan amplifier detector was added to the apparatus for certain measurements. The cells were of the Hartley–Barrett type (*J.*, 1913, **103**, 786), made of borosilicate glass and fitted with greyed platinum electrodes. The solvents were freshly distilled and all solutions were made up by weight. "Dilution run" techniques were used, five or six experimental points were obtained per run and the runs were so arranged that considerable overlap of experimental points was obtained. In order to prevent access of air and impurities the apparatus was all-glass and solvents and solutions were manipulated by the "blowing-over" technique with dry nitrogen. Solvent corrections were usually negligible, the mixed solvents having conductivities of the same order as the pure organic liquids.

Measurements were made at approx. 1, 1·5, and 3 kc./sec. but no polarisation effects were detected.

Materials.—Water of specific conductivity better than 0·6 gemmho was used. The electrolytes were recrystallised several times from such conductivity water.

The solvents were purified as described by Griffiths (*J.*, 1952, 1326) and the physical constants of the mixtures were taken from sources given by him (*J.*, 1954, 686). Particular care was paid to the drying of the acetone (Dippy and Hughes, *J.*, 1954, 953) and Karl Fischer determinations of moisture were made by the method described by Mitchell and Smith ("Aquametry," Interscience Publ., New York, 1948), and purification was continued until the acetone was dry. It was found that as the solvent became progressively drier, the salt became more and more difficult to dissolve in it, and high concentrations of electrolyte could not be obtained (see Griffiths and Lawrence, *loc. cit.*).

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BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, December 21st*, 1954.]

The Preparation of Aldotetroses from Aldopentoses via 1 : 1-*Diethylsulphonyl*-3 : 4 : 5-*trihydroxypent*-1-*enes*.

By L. HOUGH and T. J. TAYLOR.

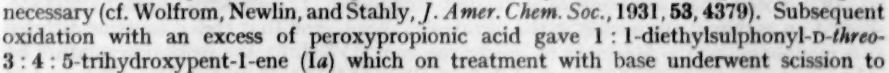
[Reprint Order No. 5921.]

Aldopentose diethyl dithioacetals are oxidised by aqueous peroxypropionic acid to 1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxypent-1-enes (I; R = trihydroxypropyl) which on treatment with dilute ammonia solution are degraded in high yield to the corresponding aldotetroses. A preliminary account of this work has appeared elsewhere (Hough and Taylor, *Chem. and Ind.*, 1954, 575).

CONVENTIONAL methods of aldose degradation when applied to the preparation of aldotetroses from aldopentoses are not wholly satisfactory. The yields are generally poor, owing to over-oxidation and epimerisation, and the products are of doubtful purity unless subsequently purified either by chromatography or through crystalline derivatives. Deulofeu (*Adv. Carbohydrate Chem.*, 1949, **4**, 119) and Hockett (*J. Amer. Chem. Soc.*, 1935, **57**, 2260, 2265) have summarised the early work and described some improvements of the Ruff, Wohl, and Zemplén degradations. In the Ruff degradation, which has been improved by use of ion-exchange resins (Diehl, Fletcher, and Hudson, *ibid.*, 1950, **72**, 4546), over-oxidation gives a mixture of triose and tetrose (unpublished observations by J. K. N. Jones and K. B. Taylor) which require separation either by chromatography on cellulose or by fractional distillation of volatile derivatives (Overend, Stacey, and Wiggins, *J.*, 1949, 1358). Hexose oximes have been degraded to pentoses in good yield by 1-fluoro-2 : 4-dinitrobenzene (Weygand and Löwenfeld, *Ber.*, 1950, **83**, 559), but details have not yet been

published of its application to the preparation of tetroses. 3 : 4-Dihydro-3 : 4-dihydroxypyrans (pentals) can be ozonised in acetic acid to tetroses, but the method is tedious and the overall yields low (Freudenberg, *Ber.*, 1932, **65**, 168; Felton and Freudenberg, *J. Amer. Chem. Soc.*, 1935, **57**, 1637). An excellent method for the degradation of D-mannose has been described by McDonald and Fischer (*Biochim. Biophys. Acta*, 1953, **12**, 203) whereby diethylsulphonyl derivatives of the aldose, obtained by oxidation of its diethyl dithioacetal with peroxypropionic acid, are converted in almost quantitative yield into D-arabinose and diethylsulphonylmethane, by treatment with aqueous ammonia. This method is a simplification of that previously described for the degradation of 3 : 4 : 5 : 6-tetra-*O*-acetyl-1 : 1-diethylsulphonylhex-1-enes to pentoses (McDonald and Fischer, *J. Amer. Chem. Soc.*, 1952, **74**, 2087), and D-*arabo*-1 : 3 : 4 : 5 : 6-penta-*O*-acetyl-2 : 2-diethylsulphonylhexane to D-erythrose bisacetamide (Bourne and Stephens, *J.*, 1954, 4009).

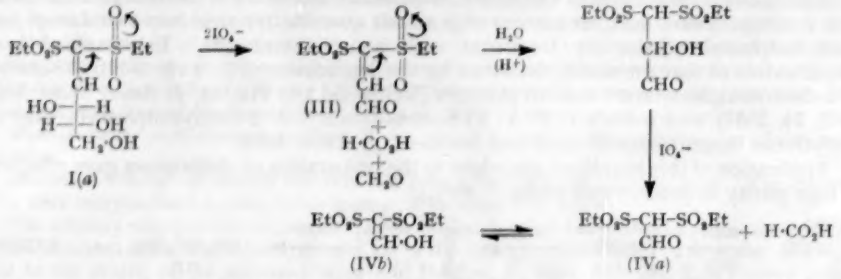
Application of this simplified procedure to the preparation of aldetetroses gave products of high purity in good overall yields (>60%).



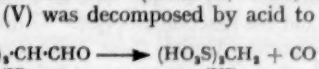
Crystalline D-xylose diethyl dithioacetal was prepared directly from D-xylose, ethanethiol, and concentrated hydrochloric acid, purification *via* acetylation and deacetylation being unnecessary (cf. Wolfrom, Newlin, and Stahly, *J. Amer. Chem. Soc.*, 1931, **53**, 4379). Subsequent oxidation with an excess of peroxypropionic acid gave 1 : 1-diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene (I*a*) which on treatment with base underwent scission to D-threose and diethylsulphonylmethane (II). Good yields of tetrose were obtained by use of dilute aqueous ammonia (pH 9—10), but as formation of tetrose proceeded the pH gradually fell to 3—4 and the reaction stopped. Consequently ammonia was added at intervals to ensure completion. Under these conditions a chromatographically pure product was obtained, but when stronger ammonia solution (pH >10) was used, epimerisation and degradation of the tetrose were observed. The hydroxyl form of Amberlite IR-4B resin was also used to cleave the disulphone. A product of high purity, as indicated by paper chromatography, was isolated, but in comparatively poor yield (*ca.* 25%). This may be attributed to a chemical combination of the tetrose or its precursor with the resin, since a further quantity of tetrose (*ca.* 50% of the theoretical amount) could be isolated on treatment of the resin with excess of 0·5N-sulphuric acid. By use of the carbonate form of Amberlite IR-4B resin, similar results were obtained, but yields were lower. However, it has been shown that little or no tetrose is removed on shaking an aqueous solution with the hydroxyl form of Amberlite IR-4B resin, under the conditions used in the degradation. D-Threose formed a highly crystalline benzoylhydrazone which should prove useful for the characterisation of this sugar.

The presence of a double bond in the diethylsulphonylpentene (I*a*) was suggested by its absorption in the ultraviolet region below 215 mμ in 95% ethanol and by mild hydrogenation to form a dihydro-derivative, 1 : 1-diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypentane. Acetylation gave D-*threo*-3 : 4 : 5-tri-*O*-acetyl-1 : 1-diethylsulphonylpent-1-ene, which, like the 3 : 4 : 5 : 6-tetra-*O*-acetyl-1 : 1-diethylsulphonylhex-1-enes, was not degraded when treated with ammonia solution (*d* 0·88) in methanol. Addition at the double bond occurred, forming a 2-amino-1 : 1-diethylsulphonyl derivative, which was isolated as its crystalline tri-*O*-acetyl derivative. The diethylsulphonylpentene (I*a*) neither gave a colour reaction with tetranitromethane nor decolorised bromine in chloroform, but it gave a magenta colour reaction in pyridine solution. The absence of olefinic properties may be attributed to removal of anionoid character from $C_{(1)}$ by the adjacent strongly electrophilic ethylsulphonyl groups. However, $C_{(2)}$ is cationoid and this accounts for the sensitivity of the molecule towards hydroxyl ions and other anionoid groups. A molecular model (Catalin Ltd.) of (I; R = trihydroxypropyl) shows that the double bond is strained. Furthermore, the ethylsulphonyl groups sterically hinder one another, and one of them is also hindered by the hydroxyl group on $C_{(3)}$. Despite this hindrance, $C_{(2)}$ remains clear for hydroxyl-ion attack.

Periodate oxidation of 1 : 1-diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene gave unusual results. Three mols. of periodate were consumed at room temperature and in the dark, with the formation of one mol. of formaldehyde and three equivalents of acid, two of which were formic acid. It has been suggested that the acid which was not volatile in steam was the enolic form (IV*b*) of diethylsulphonylacetaldehyde (IV*a*), formed together



with one mol. of formic acid by oxidation of the αβ-unsaturated aldehyde (III) with one mol. of metaperiodate (Hough and Taylor, *loc. cit.*). Böhme and Wolff (*Ber.*, 1947, **80**, 193) noted that solutions of a related compound, 1 : 1-dimethylsulphonylacetone, showed no carbonyl absorption in the ultraviolet region, and that this compound titrated as a monobasic acid. Attempts to isolate the enol (IV*b*) from the oxidation mixture by chloroform extraction were unsuccessful, only diethylsulphonylmethane being obtained on evaporation of the chloroform. Schröeter (*Annalen*, 1898, **303**, 123) observed that formylmethanedisulphonic acid (V) was decomposed by acid to methanedisulphonic acid



(VI) and carbon monoxide. Since formic acid was also taken into the chloroform with (IV), it probably caused decomposition of (IV) into carbon monoxide and diethylsulphonylmethane. Diethylsulphonylmethane rapidly decolourises aqueous iodine in the presence of saturated sodium hydrogen carbonate solution; hence this compound was not present in the original samples taken from the periodate oxidation mixture, as no fading end-points were observed during estimations of periodate uptake by Fleury and Lange's method (*J. Pharm. Chim.*, 1933, **17**, 196; cf. Schwarz, *Chem. and Ind.*, 1954, 1000). Results obtained by the latter method were completely compatible with those obtained by the thiosulphate method (Hughes and Nevell, *Trans. Faraday Soc.*, 1948, **44**, 941). Also this observation indicates that (IV) does not interfere with the Fleury–Lange estimation (cf. Schwarz, *loc. cit.*; Bonner and Drisko, *J. Amer. Chem. Soc.*, 1951, **73**, 3699), probably because it exists in solution as the enol (IV*b*) which has no active hydrogen atom.

Diethylsulphonylmethane was not oxidised by metaperiodate, despite activation of the methylene group by the adjacent ethylsulphonyl groups. This is of interest in view of the suggestions that substituted malondialdehyde systems are oxidised at the active hydrogen atom (cf. Huebner, Ames, and Bubl, *ibid.*, 1946, **68**, 1621; Sprinson and Chargaff, *J. Biol. Chem.*, 1946, **164**, 433), as has been often suggested to account for the over-oxidation of carbohydrates (*e.g.*, Neumüller and Vasseur, *Arkiv Kemi*, 1953, **5**, 235; Head and Hughes, *J.*, 1954, 603). It has been established that an adjacent *free* carboxyl, but not ester group, is necessary for oxidation by periodate of the activated hydrogen to hydroxyl; thus, malonic acid, but not diethyl malonate, is oxidised (Huebner, Ames, and Bubl, *loc. cit.*). However, the evidence for a free aldehyde group is rather inconclusive.

It is also noteworthy that the acetylated 3 : 4 : 5-trihydroxy-1-nitropent-1-enes and 3 : 4 : 5 : 6-tetrahydroxy-1-nitrohex-1-enes, obtained by the action of mild base on the corresponding nitro-alcohols (*e.g.*, Schmidt and Rutz, *Ber.*, 1928, **61**, 2142; Sowden and Fischer, *J. Amer. Chem. Soc.*, 1947, **69**, 1048), bear a structural similarity to the acetylated 1 : 1-diethylsulphonyl-3 : 4 : 5 : 6-tetrahydroxyhex-1-enes (McDonald and Fischer, *loc.*

cit.) and the 1 : 1-diethylsulphonyl-3 : 4 : 5-trihydroxypent-1-enes. However, these unsaturated nitro-compounds are not degraded under mild alkaline conditions and the electrophilic character of the single nitro-group is apparently insufficient to provide the necessary cationoid activity at $C_{(2)}$. A molecular model of this type of compound indicates that the double bond is not strained.

D-Arabinose and D-ribose diethyl dithioacetals were oxidised by an excess of aqueous peroxypropionic acid to 1 : 1-diethylsulphonyl-D-*erythro*-3 : 4 : 5-trihydroxypent-1-ene (I; R = D-*erythro*trihydroxypropyl), which was converted in high yield into D-erythrose and diethylsulphonylmethane. This pentene derivative showed end absorption in the ultraviolet region, was hydrogenated under mild conditions, and gave a magenta colour in pyridine solution.

Experimental

Microanalyses were by Mr. B. S. Noyes of Bristol. Evaporations were under reduced pressure. Paper chromatography was performed by the descending method at room temperature on Whatman No. 1 filter paper with *n*-butanol–pyridine–water (10 : 3 : 3; v/v) as mobile phase and by use of ammoniacal silver nitrate for the detection of the polyhydroxy-compounds. R_f values are approximate. M. p.s of the disulphones were determined on a Kofler microheating stage, since in glass tubes these compounds melted over a wide range, presumably because alkali in the glass degraded them.

D-*Xylose Diethyl Lithioacetal.*—D-Xylose (6 g.) was shaken with ice-cold concentrated hydrochloric acid (6 ml.) and ice-cold ethanethiol (6 g.) until a homogeneous mixture was obtained. After 6 hr., the mixture was diluted with methanol (25 ml.) and neutralised with lead carbonate. The insoluble lead salts were filtered off and washed with boiling methanol (100 ml.). Concentration of the combined filtrate and washings yielded a pale yellow syrup which was twice dissolved in methanol, filtered, and reconcentrated, to leave D-xylose diethyl dithioacetal (8·2 g.; 80%). The sticky crystals were triturated with ether and dried on a porous tile. Recrystallised from methanol–ether, they had m. p. 69—71°, R_f 0·70 (white-centred spot) (Found: C, 42·1; H, 7·5. Calc. for $C_9H_{20}O_4S_2$: C, 42·1; H, 7·8%). (Wolfrom, Newlin, and Stahly, *loc. cit.*, reported m. p. 63—65°.)

Peroxypropionic Acid (d'Ans and Frey, *Ber.*, 1912, **45**, 1845).—Propionic anhydride (30 g.) was mixed with hydrogen peroxide (90—100 vol.; 30 ml.), and to the mixture was added one drop of concentrated sulphuric acid. Usually a vigorous reaction ensued with the evolution of pungent irritating vapour. The mixture was cooled to room temperature; if another drop of acid caused no further vigorous reaction, concentrated sulphuric acid (15 ml.) was carefully added, and then hydrogen peroxide (90—100 vol.; 30 ml.). After 12 hr. at room temperature, the mixture was distilled at 25—30°/15 mm. The aqueous distillate contained sufficient peroxypropionic acid for the oxidation of 10—15 g. of pentose diethyl dithioacetal.

Peroxypropionic acid was extremely painful to the skin.

1 : 1-*Diethylsulphonyl*-D-threo-3 : 4 : 5-*trihydroxypent*-1-*ene.*—To a solution of D-xylose diethyl dithioacetal (7·1 g.) in dioxan (20 ml.) was added, dropwise with shaking, excess of aqueous peroxypropionic acid (150% of theory for 4 mols., based on propionic anhydride). After 10 min. at room temperature, the mixture was cooled in ice for 1 hr. Subsequent concentration yielded a syrup which partially crystallised. To remove traces of peroxypropionic acid, this was twice dissolved in methanol and reconcentrated. It was then crystallised twice from methanol, giving needles of 1 : 1-*diethylsulphonyl*-D-threo-3 : 4 : 5-*trihydroxypent*-1-*ene* (7·9 g.; 94%), m. p. 109—111°, $[\alpha]_D$ +23·8° (*c*, 2·26 in MeOH), R_f 0·72 (Found: C, 35·9; H, 5·8. $C_9H_{18}O_7S_2$ requires C, 35·8; H, 5·9%). Some preparations failed to crystallise, but the syrups were satisfactorily degraded to D-threose in good yield.

D-*Threose.*—(i) 1 : 1-Diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene (4·7 g.) was dissolved in dilute aqueous ammonia (50 ml.; pH 9—10); immediately the solution assumed a yellow colour which rapidly darkened to orange-red. The pH gradually fell to 3—4 and at intervals (initially ½ hr.) had to be restored with more ammonia solution. Paper chromatography indicated that degradation was complete in 48 hr. Diethylsulphonylmethane was removed by filtration and the solution de-ionised with Amberlite IR-120 and IR-4B resins (see Bayly, Bourne, and Stacey, *Nature*, 1951, **168**, 510; 1952, **169**, 876). The neutral solution was then extracted continually with chloroform to remove any remaining diethylsulphonylmethane. Concentration of the aqueous layer yielded a pale yellow syrup of D-threose (1·7 g.; 91%; 68% based on D-xylose), $[\alpha]_D$ −11° (*c*, 2·50 in H_2O). Hockett (*loc. cit.*) quoted $[\alpha]_D$

−12·3° (cf. Hockett, Deulofeu, and Mendive, *J. Amer. Chem. Soc.*, 1938, **60**, 278). The product gave one spot (R_f 0·40) only on the paper chromatogram; erythrose (R_f 0·32) and *glycero*-tetrulose (R_f 0·36), which are distinguishable from threose, could not be detected.

(ii) 1 : 1-Diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene (1 g.) in water (10 ml.) was shaken at room temperature with Amberlite IR-4B (hydroxyl form) resin (2 g.) until paper chromatography of the aqueous phase indicated that degradation was complete (*ca.* 2 days). After filtration, the resin was washed by shaking it with water (2 × 50 ml.) for 1—2 hr., then the neutral solution and washings were extracted continuously with chloroform to remove diethylsulphonylmethane. Concentration yielded a colourless syrup of D-threose (0·10 g.; 26%). Further washings with water did not contain threose. Then the resin was shaken with 0·5N-sulphuric acid (100 ml.) for 18 hr., followed by water (50 ml.) for 1—2 hr. After neutralisation ($BaCO_3$), the combined washings were extracted continuously with chloroform to remove any diethylsulphonylmethane. Subsequent concentration yielded a pale yellow syrup of D-threose (0·19 g.; 49%). Both samples of D-threose gave only one spot (R_f 0·40) on the paper chromatogram, but the material obtained from acid washing of the resin showed some impurity which remained on the starting line. The tetroses gave yellow spots with *p*-anisidine hydrochloride spray.

D-Threose phenylosazone had m. p. 164—165° (Found: C, 64·4; H, 6·3; N, 18·9. Calc. for $C_{16}H_{18}O_3N_4$: C, 64·4; H, 6·1; N, 18·8%). D-Threose gave a highly crystalline *benzoylhydrazone* when heated with benzoylhydrazine in a minimum of ethanol at 95—100° for 1 hr. and then cooled. Recrystallisation from ethanol gave fine needles, m. p. 167—168° (decomp.) (Found: C, 55·3; H, 5·9 N, 12·0. $C_{11}H_{14}O_4N_2$ requires C, 55·4; H, 5·9; N, 11·8%).

1 : 1-*Diethylsulphonyl*-D-threo-3 : 4 : 5-*trihydroxypentane*.—1 : 1-Diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene (0·57 g.) in 95% ethanol (15 ml.) was hydrogenated at atmospheric pressure and room temperature in the presence of Raney nickel (5 g.). One mol. of hydrogen was consumed in 45 min. After removal of the catalyst, concentration of the solution yielded a syrup (0·49 g.) which was crystallised twice from methanol; the *pentane* (0·47 g., 82%) had m. p. 111—113°, $[\alpha]_D$ +28·6° (*c*, 1·31 in MeOH), R_f 0·63 (Found: C, 35·5; H, 6·4. $C_9H_{20}O_7S_2$ requires C, 35·5; H, 6·6%).

D-threo-3 : 4 : 5-*Tri*-O-*acetyl*-1 : 1-*diethylsulphonylpent*-1-*ene*.—A solution of 1 : 1-diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene (0·24 g.) in acetic anhydride (5 ml.) containing one drop of concentrated sulphuric acid was heated at 95—100° for ½ hr., and then poured into ice-water. An oil separated; this was extracted with chloroform (2 × 50 ml.), and the extract was washed with sodium carbonate solution and water, and dried ($MgSO_4$). Subsequent concentration of the solution gave a pale yellow syrup (0·28 g.; 80%) of the tri-*O*-acetyl derivative, $[\alpha]_D$ −11·6° (*c*, 8·05 in $CHCl_3$).

2-*Acetamido*-D-threo-3 : 4 : 5-*tri*-O-*acetyl*-1 : 1-*diethylsulphonylpentane*.—D-*threo*-3 : 4 : 5-Tri-*O*-acetyl-1 : 1-diethylsulphonylpent-1-ene (0·10 g.) was dissolved in a mixture of ammonia solution (2 ml.; *d* 0·88) and methanol (2 ml.) and set aside at room temperature for 18 hr. A paper chromatogram displayed only one spot (R_f 0·65), presumably due to 2-acetamido-1 : 1-diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypentane (cf. Bourne and Stephens, *loc. cit.*). Concentration yielded a pale yellow syrup which was dried by repeated dissolution in ethanol and reconcentration. The syrup was then acetylated as above. Concentration of the chloroform extract gave a pale yellow syrup which crystallised spontaneously. Recrystallised from ethanol, it gave *needles* (0·056 g.; 46%), m. p. 122—123°, $[\alpha]_D$ +12·9° (*c*, 1·35 in $CHCl_3$) (Found: C, 42·0; H, 6·0; N, 3·0. $C_{17}H_{29}O_{11}S_2N$ requires C, 41·8; H, 6·0; N, 2·9%).

D-*Arabinose Diethyl Dithioacetal* (Fischer, *Ber.*, 1894, **27**, 673).—D-Arabinose (5 g.) was shaken with concentrated hydrochloric acid (5 ml.) and ethanethiol (5 g.) until the crude D-arabinose diethyl dithioacetal separated. After 2 hr., the product was filtered off, washed with light petroleum (b. p. 40—60°), and recrystallised from methanol (5·4 g., 64%); it had m. p. 127—128°, R_f 0·78 (white-centred spot).

D-*Ribose Diethyl Dithioacetal*.—Prepared from D-ribose (1 g.) as for D-xylose diethyl dithioacetal. Paper chromatography showed that the syrupy product (1·5 g.) contained impurities with R_f 0·65 and 0·70 in addition to D-ribose diethyl dithioacetal (R_f 0·79; white-centred spot). After several days, the syrup crystallised; recrystallised from methanol–ether it (1·4 g., 80%) had m. p. 80—82°. Kenner, Rodda, and Todd (*J.*, 1949, 1616) record m. p. 82—83°.

1 : 1-*Diethylsulphonyl*-D-erythro-3 : 4 : 5-*trihydroxypent*-1-*ene*.—(i) D-Arabinose diethyl dithioacetal (5·4 g.) was oxidised as for D-xylose diethyl dithioacetal giving a syrup (6·1 g.) which crystallised during 2 weeks. Recrystallisation (methanol) gave needles of 1 : 1-*diethylsulphonyl*-D-erythro-3 : 4 : 5-*trihydroxypent*-1-*ene* (5·9 g., 92%), m. p. 108—110°, $[\alpha]_D$ −58° (*c*, 2·29 in

MeOH), R_f 0·72 (Found: C, 35·9; H, 5·9. $C_9H_{18}O_7S_2$ requires C, 35·8; H, 5·9%). (ii) D-Ribose diethyl dithioacetal (1·4 g.) was oxidised as for D-xylose diethyl dithioacetal. A syrup (1·6 g.) was obtained which slowly crystallised. Paper chromatography indicated traces of erythrose, presumably produced by degradation of the diethylsulphonyl derivative. Crystallisation from methanol gave material (1·5 g., 90%), m. p. 105—107°, $[\alpha]_D$ −64° (*c*, 1·68 in MeOH), R_f 0·72. *X*-Ray powder photographs of the crystals, obtained from the oxidation of D-arabinose and D-ribose diethyl dithioacetals, were identical and a mixture of the two crystalline products had m. p. 107—109°.

D-*Erythrose*.—1 : 1-Diethylsulphonyl-D-*erythro*-3 : 4 : 5-trihydroxypent-1-ene (5·4 g.) was degraded as for 1 : 1-diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene giving a pale yellow syrup of D-erythrose (1·9 g., 89%; 52% based on D-arabinose; 64% based on D-ribose) which gave one spot (R_f 0·32) on the paper chromatogram, indicating the absence of threose and *glycero*tetrulose. It had $[\alpha]_D$ −15·9° ⟶ −23·1° (48 hr.; *c*, 1·89 in H_2O) which is higher than reported for the D-isomer; cf. Overend, Stacey, and Wiggins (*loc. cit.*), −18·5°; Ruff (*Ber.*, 1899, **32**, 3672), −14·8°. It is, however, within the numerical range of values reported for the L-isomer; cf. Felton and Freudenberg (*loc. cit.*), +30·5°; Wohl (*Ber.*, 1899, **32**, 3667), +32·7°; Weerman (*Rec. Trav. chim.*, 1917, **37**, 16), +23·6°; Deulofeu (*J.*, 1932, 2973), +22·1°; Ruff (*Ber.*, 1901, **34**, 1365), +21·5°.

D-Erythrose was converted into its phenylosazone which had m. p. 164—165° (Found: C, 64·4; H, 6·2; N, 18·5. Calc. for $C_{16}H_{20}O_2N_4$: C, 64·4; H, 6·1; N, 18·8%). D-Erythrose did not form a crystalline benzoylhydrazone.

1 : 1-*Diethylsulphonyl*-D-erythro-3 : 4 : 5-*trihydroxypentane*.—1 : 1-Diethylsulphonyl-D-*erythro*-3 : 4 : 5-trihydroxypent-1-ene (0·66 g.) was hydrogenated as for 1 : 1-diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene. A pale yellow syrup of the hydrogenated material (0·68 g.; R_f 0·64) could not be induced to crystallise.

Periodate Oxidation of 1 : 1-*Diethylsulphonyl*-D-threo-3 : 4 : 5-*trihydroxypent*-1-*ene*.—A mixture of *ca.* 0·3M-sodium metaperiodate (4 ml.) and 1 : 1-diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene (53·3 mg.) in water (5 ml.) was made up to 50 ml. and stored in an amber bottle in the dark. A blank, containing none of the disulphone, was worked concurrently. Samples were taken at intervals for determination of periodate and acid. Two methods for measuring the uptake of sodium metaperiodate were used.

(i) *Arsenite method* (Fleury and Lange, *loc. cit.*). Samples (5 ml.) were taken from the oxidation mixture and from the blank. To each was added saturated sodium hydrogen carbonate solution (10 ml.), *ca.* 0·1N-sodium arsenite solution (4 ml.), and 20% potassium iodide solution (4 ml.). After 15 min., excess of arsenite was titrated with 0·01N-iodine, starch being used as indicator. The end points were sharp.

(ii) *Thiosulphate method* (Hughes and Nevell, *loc. cit.*). Samples (5 ml.) were taken from the oxidation mixture and from the blank. To each was added 2N-sulphuric acid (5—10 ml.) and then 20% potassium iodide (4 ml.). The iodine liberated was titrated with 0·01N-sodium thiosulphate, starch being used as indicator.

Total acidity (Halsall, Hirst, and Jones, *J.*, 1947, 1427) was determined by taking samples (5 ml.) from the oxidation mixture and from the blank, adding ethylene glycol (2 ml.) to each, and 5 min. later, titrating with 0·01N-sodium hydroxide, with methyl red (screened with methylene blue) as indicator.

Formic acid produced was determined by steam distillation of samples (10 ml.) treated with ethylene glycol as above, and titration of the distillate (*ca.* 50 ml.) with 0·01N-sodium hydroxide.

Formaldehyde was determined by Bell's method (*J.*, 1948, 992) but with a phosphate buffer of pH 6·98. 1 : 1-Diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene (17·5 mg.) gave 15·6 mg. of the formaldehyde derivative (m. p. 187—188°), equivalent to 0·92 mol. of formaldehyde liberated.

Results are in the Table.

Time, hr.	$NaIO_4$, uptake, mol., arsenite	$NaIO_4$, uptake, mol., thiosulphate	Total acid, equiv.	$H{\cdot}CO_2H$, equiv.
3	2·36	2·37	2·23	—
6	2·55	2·62	2·52	—
24	2·95	2·91	2·76	2·03

Attempted Isolation of Diethylsulphonylacetaldehyde (IV*a*).—An aqueous solution (200 ml.) containing 1 : 1-diethylsulphonyl-D-*threo*-3 : 4 : 5-trihydroxypent-1-ene (2·2 g.) and sodium metaperiodate (5 g.) was stored in an amber bottle in the dark for 24 hr. The solution was

extracted with chloroform (6 × 100 ml.), and the combined extracts dried (Na_2SO_4) and concentrated at room temperature to an acidic syrup (0·5 g.) which rapidly crystallised. Recrystallised from methanol, the product had m. p. 100—102°, not depressed on admixture with authentic diethylsulphonylmethane (Found: C, 30·2; H, 5·7. Calc for $C_5H_{12}O_4S_2$: C, 30·0; H, 6·0%).

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The Acidity Function H_0 for Solutions of Trifluoroacetic Acid and Trichloroacetic Acid in Water.

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The acidity function H_0 has been determined for solutions of trifluoroacetic and trichloroacetic acid in water. The readings show that, although in very dilute aqueous solution both acids are barely distinguishable from strong acids, in more concentrated solutions they are appreciably associated. In concentrations greater than 25%, the dielectric constant of the solution appears to have an appreciable effect on the acidity, as measured by H_0, the effect being more marked with trichloroacetic than with trifluoroacetic acid solutions.

THE acidity function H_0, introduced by Hammett and Deyrup (*J. Amer. Chem. Soc.*, 1932, **54**, 2721), measures the tendency of a solution to donate a proton to a neutral base.

$$H_0 = pK + \log([B]/[BH^+]) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

This function has proved of considerable value in studies of the mechanism of acid-catalysed reactions, and its use has recently received considerable attention. In searching for a tool with which to study the mechanism of the synthetic reactions of trifluoroacetic anhydride, it was thought that the determination of the acidity function of various solutions of trifluoroacetic acid might prove of value, particularly in view of Mackenzie and Winter's studies (*Trans. Faraday Soc.*, 1948, **44**, 159) of the acidity function in acetic anhydride solutions. Previous work on the acidity of trifluoroacetic acid has been confined to conductometric measurements in dilute solution and the determination of the classical aqueous dissociation constant (Swarts, *Bull. Acad. roy. Belg.*, 1922, **6**, 352; Henne and Fox, *J. Amer. Chem. Soc.*, 1951, **73**, 2323). The only carboxylic acids for which the values of H_0 have been determined are pure and very concentrated formic acid (Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 4239) and trichloroacetic acid in relatively dilute solution (Hammett and Paul, *J. Amer. Chem Soc.*, 1934, **56**, 827).

Before describing the results of the present work, a very brief consideration of the properties of H_0 itself will greatly help to clarify subsequent discussion. In a system consisting of an acid HA in a solvent S with a neutral base B, the following equilibria are present:

$$HA + S \rightleftharpoons HS^+ + A^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$HS^+ + B \rightleftharpoons HB^+ + S \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$HA + B \rightleftharpoons HB^+ + A^- \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Equation (4) is contained in equations (2) and (3). Since $K = a_B a_{H^+}/a_{BH^+}$ (cf. Hammett and Deyrup, *loc. cit.*), equation (1) can be rearranged to

$$H_0 = -\log a_{H^+} - \log(f_B/f_{HB^+}) \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Throughout this discussion, dissociation constants and activity coefficients are to be referred to the standard state of infinitely dilute aqueous solution. Two extreme types of acid solution can be envisaged. When HA is a strong acid completely dissociated the following approximate equation can be written for dilute solutions:

$$H_0 \approx -\log [\text{Total Acid}] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

and when HA is a weak acid completely associated:

$$H_0 \approx -\tfrac{1}{2}\log [\text{Total Acid}] - \tfrac{1}{2}\log K_{HA} \quad . \quad . \quad . \quad . \quad . \quad (7)$$

In these equations we neglect the activity of the solvent, and take the activity coefficients of all other constituents to be unity; they can therefore only be expected to apply in very dilute aqueous solution. Under such conditions and for small changes in concentration, H_0 plotted against the logarithm of the total acid concentration may be expected to give a curve whose maximum slope should approach unity when the acid is completely dissociated, and should diminish to a minimum of a half if the acid becomes largely associated while the solution is still relatively dilute. In concentrated solutions, the activity coefficients are changing rapidly so that these predictions will no longer hold.

Fig. 1 represents H_0 plotted against percentage composition for the systems $CF_3{\cdot}CO_2H$–H_2O, and $CCl_3{\cdot}CO_2H$–H_2O. Comparison of Fig. 1 with the curves previously reported for perchloric and sulphuric acid (Hammett and Deyrup, *loc. cit.*) and for phosphoric acid (Heilbronner and Weber, *Helv. Chim. Acta*, 1949, **32**, 1513) gives the impression that trifluoroacetic acid behaves very similarly to the strong acids, while trichloroacetic acid behaves anomalously. However the similarity between the curve for trifluoroacetic acid and that of the mineral acids is somewhat superficial as can be seen from Fig. 2, where H_0 is plotted against the logarithm of the acid concentration expressed in mole fractions. It will be seen that, in the dilute solutions, the values for the acidity functions of the mineral acids coincide, forming a linear plot, the slope of which is nearly unity, as predicted by the above discussion. At greater concentrations the activity coefficients are changing rapidly and the curves slope upwards steeply. In dilute solutions of the carboxylic acids the curve of the acidity function approaches that of the mineral acids both in the slope of the curve and in actual value. As the solutions become more concentrated, however, the slopes of their acidity curves become less, clearly indicating that the acids are appreciably associated. This is fully in accord with expectations since the classical dissociation constants of both these acids are known and are less then unity. The slope of the trifluoroacetic acid curve decreases, until between the concentrations 0·03 mole fraction and 0·15 mole fraction it is approximately linear with a slope of nearly a half. This, according to the above discussion, would indicate that the acid is almost completely associated in this region. Assuming this to be so, an approximate value of 0·7 for the dissociation constant of trifluoroacetic acid can be calculated from equation (7). This is in reasonable agreement with value of 0·59 obtained by Henne and Fox (*loc. cit.*) using a much more precise method. Though it appears, on a preliminary inspection, that the behaviour of the acidity function for solutions of trifluoroacetic acid is in accord with the initial discussion, this is not the case with trichloroacetic acid. Between the concentration 0·03 mole fraction and 0·1 mole fraction, Fig. 2 (25—50%, Fig. 1), the acidity

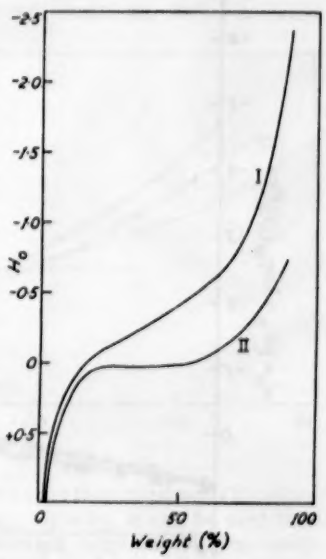
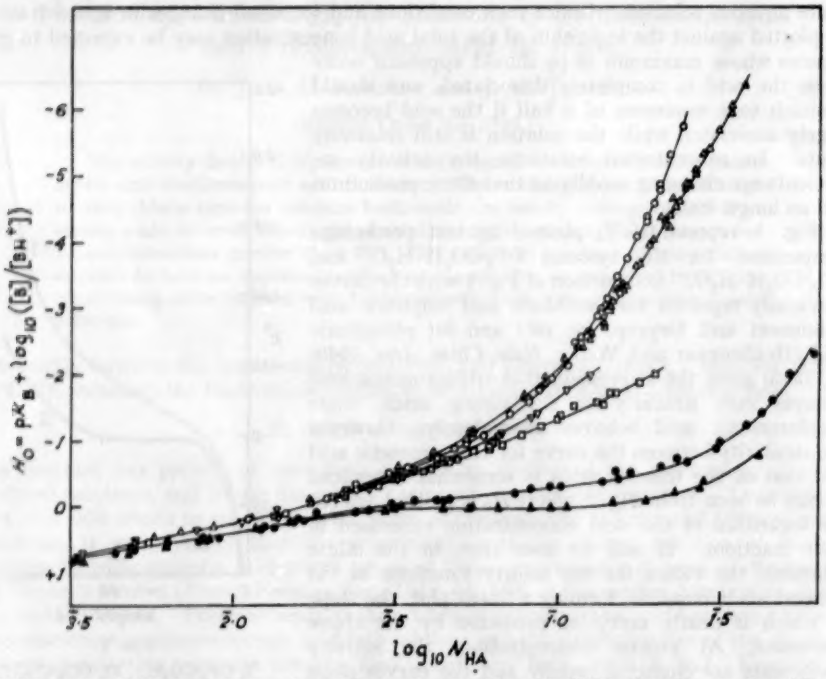


FIG. 1.

I, $CF_3{\cdot}CO_2H$. II, $CCl_3{\cdot}CO_2H$.

function remains constant instead of increasing along a line parallel to that of trifluoroacetic acid as would be expected from equation (7). This exceptional behaviour of trichloroacetic acid was first observed by Hammett and Paul (*loc. cit.*) who offered no comment (the actual value of H_0 when constant, reported by these workers, is considerably higher, *i.e.*, the acidity less, then that reported here). Experiments have been made to ensure that the observed concentrations of the indicator, by which H_0 was determined, were real concentrations and that medium effects were not altering the validity of the optical measurements (see p. 1222). Hammett has drawn attention to the fact that H_0 becomes more dependent on the medium than on the intrinsic acidity of the solute acid

FIG. 2.



○ $HClO_4$ and △ H_2SO_4 (from Hammett and Deyrup). ▽ HCl and □ HNO_3 (from Hammett and Paul). ● $CF_3{\cdot}CO_2H$ and ▲ $CCl_3{\cdot}CO_2H$ (present investigation). (For density tables see "International Critical Tables," McGraw-Hill, New York, 1928, Vol. III, pp. 54, 58.)

when the dielectric constant is low. Clearly the work required for donation of a proton to a neutral base, thus creating a positive and a negative ion, is greatly increased by a decrease in dielectric constant. This problem has been discussed by James and Knox (*Trans. Faraday Soc.*, 1950, **46**, 254) but a somewhat different approach will be made here. The dielectric constant of trichloroacetic acid is very low ($\varepsilon_{60} = 4{\cdot}55$; Walden, *Z. physikal. Chem.*, 1910, **70**, 569). Thus it seems reasonable to suggest that the abnormal behaviour of the acidity function H_0 in moderately concentrated trichloroacetic acid may be explained by the rapid decrease of the dielectric constant of these solutions. If so, then the acidity function measuring the tendency of a solution to transfer a proton to a base with a negative charge, called H_- by Hammett (cf. "Physical Organic Chemistry," McGraw Hill, New York, 1940, p. 269), should be affected in the opposite manner since this process results in a neutralisation of charges. This hypothesis has been tested

experimentally by using picric acid as indicator, and the results are shown in Fig. 3. It will be seen that in dilute solution the slopes of the H_0 and H_- curves for trichloroacetic acid are identical. In the more concentrated solutions, where the slope of the H_0 curve flattens off, the slope of the H_- curve increases and seems to confirm the above hypothesis. The slope of the H_- curve of trifluoroacetic acid also becomes greater than that of the corresponding H_0 curve, but the difference between the two is less than that between the two trichloroacetic acid curves. This is in conformity with, and probably due to, the fact that the dielectric constant of trifluoroacetic acid, though fairly low ($\epsilon_{25} = 8{\cdot}2$; Dannhauser and Cole, *J. Amer. Chem. Soc.*, 1952, **74**, 6105; cf. also Tedder, *J.*, 1954, 2646), is higher than that of trichloroacetic acid.

In conclusion it can be said that neither of these carboxylic acids is as strong as is frequently suggested. Although in very dilute aqueous solution they become almost indistinguishable from strong acids, they are appreciably associated in moderate concentrations. These findings are in accord with their classical dissociation constants (trifluoroacetic acid, $K = 5{\cdot}88 \times 10^{-1}$, Henne and Fox, *loc. cit.*; trichloroacetic acid, $K = 2{\cdot}5 \times 10^{-1}$, Drucker, *Z. physikal. Chem.*, 1904, **49**, 563; 1920, **96**, 381). A recent

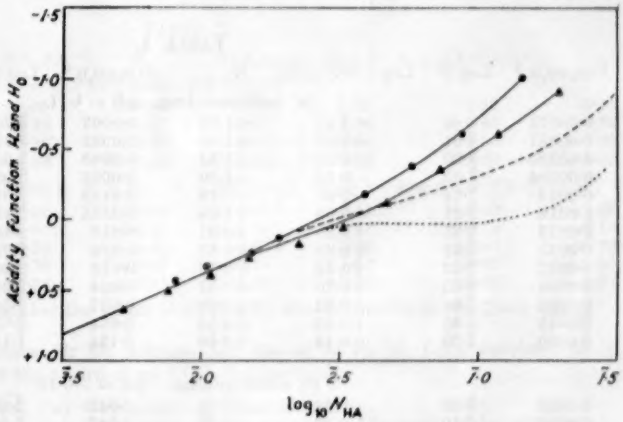


FIG. 3.
● H_- in $CF_3{\cdot}CO_2H$.
▲ H_- in $CCl_3{\cdot}CO_2H$.
– – – H_0 in $CF_3{\cdot}CO_2H$.
. . . . H_0 in $CCl_3{\cdot}CO_2H$.

suggestion that trifluoroacetic acid is nearly as strong as or stronger than nitric acid (Emeléus, Haszeldine, and Paul, *J.*, 1954, 881) is clearly misleading. Finally, it can be said that in concentrations greater than 25% in water, the low dielectric constants of these acids appear to have a considerable effect on their acidity as determined by acidity functions, and therefore this effect may also be expected to make itself felt in the catalytic properties of these solutions.

EXPERIMENTAL

H_0 was calculated from equation (1), the ratio $[B]/[BH^+]$ being determined by colorimetric measurements, and the pK of *p*-nitroaniline was taken to be 1·11 (Hammett and Paul, *loc. cit.*), while the pK of the other indicators was determined by comparison (Hammett and Deyrup, *loc. cit.*).

Preparation of the Solutions.—The appropriate indicator was first dissolved in water (*ca.* 0·02 g./l.). Two portions (10 c.c.) of this solution were placed into two graduated flasks (100 c.c.), one of which was made up to the mark with distilled water, the other with trifluoroacetic acid (or very concentrated trichloroacetic acid). A portion of the acid solution was placed in a ground-stoppered flask, to which measured portions of the aqueous solution were added from a burette. After the mixture had been shaken, a sample was withdrawn and run into a tared cell from the spectrophotometer. After the colorimetric measurements had been made, the whole cell was weighed and the solution quantitatively washed out and titrated with alkali. This served to determine the concentration of the acid in the solution, the small concentration of indicator being neglected.

Purity of the Reagents.—Commercial trifluoroacetic acid was redistilled and the centre fraction (b. p. 38·7—39·0°) was used for the acidity measurements. "AnalaR" trichloroacetic acid was used without further purification. The basic indicators were recrystallised three times from aqueous acetone; *p*-nitroaniline had m. p. 148°, *o*-nitroaniline, m. p. 71—72°, and 4-chloro-2-nitroaniline, m. p. 116—117°. Picric acid was recrystallised from hot water, and had m. p. 122—123°.

Colorimetric Measurements.—For each solution prepared as above, a solution with identical acid concentration, but without indicator, was also prepared. By using the two solutions in conjunction the extinction coefficient of the indicator solutions was obtained directly by means of a Cambridge "SP 500 Unicam" spectrophotometer ($\varepsilon = \log I/I_0$; I = transmission coefficient of the acid solution with indicator; I_0 = transmission coefficient of the same solution without indicator). Readings were taken at a fixed wave-length for any one indicator. From these readings the ratios [B]/[BH$^+$] were calculated by applying Beer's law. If ε_B, ε_{BH^+}, and ε_x are the extinction coefficients of the solution of the un-ionised base, the completely ionised base, and the unknown solution, respectively, then the indicator ratio for the unknown solution can be expressed as: $[BH^+]/[B] = (\varepsilon_B - \varepsilon_x)/(\varepsilon_x - \varepsilon_{BH^+})$ (in practice ε_{BH^+} was always negligible).

H_0 for the System Trifluoroacetic Acid–Water.—See Table 1.

TABLE 1.

$N_{CF_3\cdot CO_2H}$ *	Log N	Log ([BH$^+$]/[B])	H_0	$N_{CF_3\cdot CO_2H}$ *	Log N	Log ([BH$^+$]/[B])	H_0
		(*a*) *p*-Nitroaniline.	pK = 1·11.				
0·00071	$\bar{4}$·85	−0·44	+1·55	0·0063	$\bar{3}$·79	+0·54	+0·57
0·00081	$\bar{4}$·91	−0·39	+1·50	0·0082	$\bar{3}$·91	+0·66	+0·45
0·00100	$\bar{3}$·00	−0·22	+1·33	0·0083	$\bar{3}$·92	+0·62	+0·49
0·00104	$\bar{3}$·02	−0·18	+1·29	0·0092	$\bar{3}$·96	+0·65	+0·46
0·0014	$\bar{3}$·14	−0·07	+1·18	0·0122	$\bar{2}$·09	+0·78	+0·33
0·0016	$\bar{3}$·21	+0·05	+1·06	0·0135	$\bar{2}$·13	+0·79	+0·32
0·0023	$\bar{3}$·37	+0·20	+0·91	0·015	$\bar{2}$·19	+0·88	+0·23
0·0032	$\bar{3}$·51	+0·29	+0·82	0·016	$\bar{2}$·20	+0·90	+0·21
0·0033	$\bar{3}$·52	+0·34	+0·77	0·018	$\bar{2}$·26	+1·01	+0·09
0·0034	$\bar{3}$·53	+0·30	+0·81	0·024	$\bar{2}$·38	+1·02	+0·07
0·0044	$\bar{3}$·64	+0·43	+0·68	0·037	$\bar{2}$·56	+1·19	−0·08
0·0049	$\bar{3}$·69	+0·52	+0·59	0·074	$\bar{2}$·87	+1·31	−0·20
0·0050	$\bar{3}$·70	+0·44	+0·66	0·134	$\bar{1}$·14	+1·48	−0·37
		(*b*) *o*-Nitroaniline.	pK = −0·13.				
0·0080	$\bar{3}$·90	−0·64	+0·51	0·042	$\bar{2}$·63	−0·03	−0·10
0·0125	$\bar{3}$·10	−0·42	+0·29	0·047	$\bar{2}$·67	−0·03	−0·10
0·016	$\bar{2}$·20	−0·31	+0·18	0·083	$\bar{2}$·92	−0·14	−0·27
0·026	$\bar{2}$·42	−0·18	+0·05	0·094	$\bar{2}$·98	−0·19	−0·32
0·031	$\bar{2}$·49	−0·08	−0·05	0·150	$\bar{1}$·18	−0·41	−0·54
		(*c*) 4-Chloro-2-nitroaniline.	pK = − 0·94.				
0·045	$\bar{2}$·65	−0·85	−0·09	0·31	$\bar{1}$·49	−0·06	−0·88
0·102	$\bar{1}$·01	−0·64	−0·30	0·32	$\bar{1}$·50	+0·03	−0·97
0·155	$\bar{1}$·19	−0·51	−0·43	0·38	$\bar{1}$·58	+0·31	−1·25
0·17	$\bar{1}$·23	−0·46	−0·48	0·46	$\bar{2}$·66	+0·67	−1·61
0·21	$\bar{1}$·32	−0·33	−0·61	0·52	$\bar{1}$·71	+1·06	−2·00
0·25	$\bar{1}$·40	−0·27	−0·67	0·62	$\bar{1}$·79	+1·37	−2·31

* In this and other Tables, N = mole fraction.

H_0 for the System Trichloroacetic Acid–Water.—Several experiments were carried out to investigate the possibility that the flat portion of the trichloroacetic acid curve was due to changes in the absorption of light not directly associated with a change in the concentration of un-ionised indicator. The first possibility considered was a shift of the wave-length of the absorbing band. The absorption maximum was at 415 mμ for a solution of *p*-nitroaniline in water, in 50% trichloroacetic acid the band had shifted to 425 mμ, and in 90% acid to *ca.* 430 mμ. As the band is very broad and readings were taken at 418 mμ, this slight shift could not account for the apparent decrease in concentration of the pure base. The second possibility considered was a solvent effect causing a decrease in adsorption without any shift in the wave-length. Neutral trichloroacetate ion was found to have no effect on the absorption of the pure base. For results see Table 2.

TABLE 2.

$N_{CCl_3\cdot CO_2H}$	Log N	Log ([BH⁺]/[B])	H_0	$N_{CCl_3\cdot CO_2H}$	Log N	Log ([BH⁺]/[B])	H_0
		(*a*) *p*-Nitroaniline.		pK = 1·11.			
0·0025	$\bar{3}$·40	+0·13	+0·98	0·044	$\bar{2}$·65	+1·08	+0·03
0·0035	$\bar{3}$·54	+0·28	+0·83	0·053	$\bar{2}$·73	+1·08	+0·03
0·0047	$\bar{3}$·68	+0·40	+0·71	0·065	$\bar{2}$·82	+1·08	+0·03
0·0063	$\bar{3}$·80	+0·53	+0·58	0·083	$\bar{2}$·92	+1·08	+0·03
0·0085	$\bar{3}$·93	+0·64	+0·47	0·108	$\bar{1}$·03	+1·10	+0·01
0·012	$\bar{2}$·07	+0·81	+0·30	0·15	$\bar{1}$·17	+1·17	−0·06
0·015	$\bar{3}$·18	+0·89	+0·22	0·23	$\bar{1}$·36	+1·33	−0·22
0·031	$\bar{2}$·50	+1·08	+0·03	0·28	$\bar{1}$·45	+1·48	−0·37
		(*b*) *o*-Nitroaniline.		pK = − 0·24.			
0·0063	$\bar{3}$·80	−0·72	+0·48	0·096	$\bar{2}$·98	−0·27	+0·03
0·030	$\bar{2}$·47	−0·30	+0·06	0·19	$\bar{1}$·27	−0·15	−0·09
0·033	$\bar{2}$·52	−0·24	0·00	0·27	$\bar{1}$·44	+0·05	−0·29
0·055	$\bar{2}$·74	−0·27	+0·03	0·42	$\bar{1}$·62	+0·54	−0·78

H_- for the Systems Trifluoroacetic Acid–Water and Trichloroacetic Acid–Water.—For results see Table 3.

TABLE 3.

$N_{CF_3\cdot CO_2H}$	Log N	Log ([XH]/[X⁻])	H_-	$N_{CF_3\cdot CO_2H}$	Log N	Log ([XH]/[X⁻])	H_-
			Picric acid.	pK = 0·04.*			
0·0081	$\bar{3}$·91	−0·40	+0·44	0·039	$\bar{2}$·59	+0·22	−0·18
0·0106	$\bar{2}$·02	−0·29	+0·33	0·057	$\bar{2}$·76	+0·40	−0·38
0·015	$\bar{2}$·18	−0·20	+0·24	0·087	$\bar{2}$·94	+0·65	−0·61
0·019	$\bar{2}$·28	−0·09	+0·13	0·14	$\bar{1}$·16	+1·05	−1·01
$N_{CCl_3\cdot CO_2H}$	Log N	Log ([XH]/[X⁻])	H_-	$N_{CCl_3\cdot CO_2H}$	Log N	Log ([XH]/[X⁻])	H_-
0·0052	$\bar{3}$·72	−0·56	+0·64	0·032	$\bar{2}$·51	−0·02	+0·06
0·0076	$\bar{3}$·88	−0·47	+0·51	0·047	$\bar{2}$·67	+0·16	−0·12
0·0108	$\bar{3}$·03	−0·36	+0·40	0·073	$\bar{2}$·86	+0·40	−0·36
0·015	$\bar{3}$·17	−0·23	+0·27	0·12	$\bar{1}$·07	+0·65	−0·61
0·023	$\bar{2}$·35	−0·14	+0·18	0·20	$\bar{1}$·29	+0·95	−0·91

* This value was chosen so that the values of H_0 and H_- should coincide in the dilute region.

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Cyto-active Amino-acids and Peptides. Part II. Resolution of* para-*Substituted Phenylalanines and Synthesis of* p-*Di-*(2-*chloroethyl*)*amino-*DL-*phenyl*[β-^{14}C]*alanine.*

By F. BERGEL, V. C. E. BURNOP, and J. A. STOCK.

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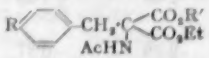
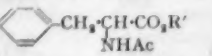
Resolution procedures for *para*-substituted phenylalanines, leading from appropriate diethyl aminomalonate derivatives to *p*-di-(2-chloroethyl)amino-L- and -D-phenylalanine, are described. DL-Phenyl[β-^{14}C]alanine and *p*-di-(2-chloroethyl)amino-DL-phenyl[β-^{14}C]alanine have been prepared.

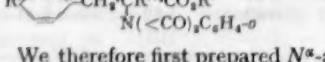
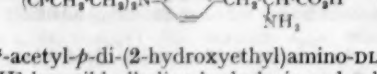
IN Part I * the syntheses of DL- (CB 3007), L- (CB 3025), and D-forms (CB 3026) of *p*-di-(2-chloroethyl)aminophenylalanine (IV) were reported. In absence of a resolution procedure the optically active compounds were made from L- and D-phenylalanine respectively; the racemic compound was prepared either from the DL-amino-acid or by the aminomalonic ester method. In view of the outstanding anti-Walker-tumour effect of

* Part I, Bergel and Stock, *J.*, 1954, 2409.

the L-isomer (cf. *Brit. Emp. Cancer Camp. Ann. Rep.*, 1953, **31**, 6), representing one of the first examples in this field of selectivity of action through optical isomerism, it became desirable to produce larger amounts of this compound for further trials, and also to synthesise a ^{14}C-labelled phenylalanine derivative for study *in vivo*.

Since the route employing the malonic ester synthesis seemed better suited to large-scale work than that starting with optically active material it was necessary to find the means of resolving one of the resulting intermediate substituted phenylalanines. It was, however, inadvisable to attempt the resolution of the final product (CB 3007) itself since halogen is readily lost from the di-(2-chloroethyl)amino-group especially under alkaline

(I)  (II) 

(III)  (IV) 

conditions. We therefore first prepared N^{α}-acetyl-*p*-di-(2-hydroxyethyl)amino-DL-phenylalanine [II; R = $(HO{\cdot}CH_2{\cdot}CH_2)_2N$, R′ = H] by mild alkaline hydrolysis and subsequent decarboxylation of the corresponding malonic ester [I; R = $(HO{\cdot}CH_2{\cdot}CH_2)_2N$, R′ = Et] (cf. Albertson, *J. Amer. Chem. Soc.*, 1950, **72**, 1396). The gummy product did not form a crystalline derivative with brucine or strychnine.

Attention was next directed to the possibility of resolving ethyl N^{α}-acetyl-*p*-amino-DL-phenylalaninate (II; R = NH_2, R′ = Et) with the aid of an optically active acid. A possible route to the amine lay in the decarboxylation of the half-ester (I; R = NH_2, R′ = H), but application of the sodium ethoxide method (Skinner and Huber, *ibid.*, 1951, **73**, 3321) to the malonate (I; R = NH_2, R′ = Et) did not yield the desired acid (I; R = NH_2, R′ = H), nor did pyridine hydrochloride in pyridine. We therefore had recourse to the alkaline hydrolysis and subsequent decarboxylation of the diester (I; R = NH_2, R′ = Et) (cf. Snyder, Shekleton, and Lewis, *ibid.*, p. 3321), which yielded N^{α}-acetyl-*p*-amino-DL-phenylalanine (II; R = NH_2, R′ = H) as a gum. This with ethanolic hydrogen chloride gave the crystalline ethyl ester (II; R = NH_2, R′ = Et) which readily formed a crystalline salt with α-bromocamphor-π-sulphonic acid, but not with tartaric or dibenzoyltartaric acid. However, the bromocamphorsulphonate did not effect a resolution.

We then prepared, from the ester (II; R = NH_2, R′ = Et), the corresponding *N*-*o*′-carboxybenzoyl derivative (II; R = o-$HO_2C{\cdot}C_6H_4{\cdot}CO{\cdot}NH$, R′ = Et) which was easily reconverted into the parent amine by hot ethanolic hydrazine. While it formed a crystalline salt with brucine, attempts to liberate the acid from this salt led to the loss of the *N*-*o*′-carboxybenzoyl group as phthalic acid. As the brucine salt itself was difficult to purify, this was not a practicable procedure. We then found that *N*-acetyl-*p*-nitro-DL-phenylalanine (II; R = NO_2, R′ = H), obtained by Albertson's (*loc. cit.*) treatment of the diester (I; R = NO_2, R′ = Et), was resolved readily with brucine in ethanol; the salt of the L-acid crystallised, leaving that of the D-isomer in the mother-liquor. The salt of the D-acid was recovered, and crystallised readily from water. *N*-Acetyl-*p*-nitro-L- and -D-phenylalanine were obtained from their salts by means of ammonia and subsequent acidification after removal of the brucine. The configurations were established by conversion of the acids into the ethyl esters (II; R = NO_2, R′ = Et), of which the L-isomer had been prepared from L-phenylalanine. Catalytic hydrogenation of the L- and D-nitro-esters gave the amino-derivatives (II; R = NH_2, R′ = Et) as gums which were characterised as their crystalline 2 : 4-dinitrophenyl derivatives. With ethylene oxide the amines gave the crystalline L- and D-di(hydroxyethyl) derivatives (II; R = $(HO{\cdot}CH_2{\cdot}CH_2)_2N$, R′ = Et). The next step towards the L-chloro-compound (IV) caused total or partial racemisation, whether phosphorus oxychloride, phosphorus pentachloride, or thionyl chloride was used as chlorinating agent. This difficulty was overcome by replacement of the *N*-acetyl by the *N*-phthaloyl group. This was done in two ways: first, by hydrolysing *N*-acetyl-*p*-nitro-L- or -D-phenylalanine (II; R = NO_2, R′ = H) to *p*-nitro-L- or -D-phenylalanine, esterifying the carboxyl group with ethanolic hydrogen

chloride, and allowing the ester to react with phthalic anhydride as described in Part I (*loc. cit.*) to form the nitro-ester (III; R = NO_2, R′ = Et, R″ = H). Reduction of the nitro-group, hydroxyethylation, chlorination, and hydrolysis led to the desired D- and L-forms (IV). The second approach began with the synthesis of diethyl α-4-nitrobenzyl-α-phthalimidomalonate. *p*-Nitrobenzyl chloride could not be condensed with diethyl phthalimidomalonate by use of sodium ethoxide in ethanol or the sodio-derivative of the phthalimidomalonic ester [prepared by means of powdered sodium in toluene or by Barger and Weichselbaum's method (*Org. Synth.*, 1943, Coll. Vol. II, p. 384)] in dioxan or in a melt containing an equivalent or an excess of halide, but the reactants gave a 85—90% yield in ethyl methyl ketone in the presence of sodium iodide. The resulting crystalline malonate (III; R = NO_2, R′ = Et, R″ = CO_2Et) was hydrolysed by Albertson's method to *N-o'*-carboxybenzoyl-*p*-nitro-DL-phenylalanine which was cyclised with acetic anhydride to *p*-nitro-*N*-phthaloyl-DL-phenylalanine (III; R = NO_2, R′ = R″ = H). This was not fully resolved by way of the brucine salt; but mixing equimolar amounts of cinchonidine and the DL-acid in methanol led to precipitation of the salt of the D-acid, whilst that of the L-acid was recoverable from the mother-liquor. Isolation of the isomeric acids and esterification gave the D- and the L-ester (III; R = NO_2, R′ = Et, R″ = H) previously described. Their rotations established the configurations of the parent acids and salts. From these esters, the optically active chloroethyl derivatives (IV) were obtained as described in Part I (*loc. cit.*).

In the following the synthesis of *p*-di-(2-chloroethyl)amino-DL-phenyl[β-^{14}C]alanine is reported. [*carboxy*-^{14}C]Benzoic acid, from phenylmagnesium bromide and ^{14}C-carbon dioxide (cf. Calvin *et al.*, "Isotopic Carbon," J. Wiley and Sons, New York, 1949, p. 180), was reduced with lithium aluminium hydride to [α-^{14}C]benzyl alcohol. With zinc chloride and hydrochloric acid this gave [α-^{14}C]benzyl chloride and thence diethyl acetamido-([α-^{14}C]benzyl)malonate (I; R = H, R′ = Et) in an overall yield of 67% from carbon dioxide. Part of this product was hydrolysed to DL-phenyl[β-^{14}C]alanine, identified by paper chromatography. Syntheses of phenylalanine labelled in other positions have been reported by Gurin and Delluva (*J. Biol. Chem.*, 1947, **170**, 545), Schepatz and Gurin (*ibid.*, 1949, **180**, 663), Lerner (*ibid.*, 1949, **181**, 281), and Henneberry *et al.* (*Canad. J. Chem.*, 1951, **29**, 229).

Nitration of the ester (I; R = H, R′ = Et) in acetic anhydride gave diethyl acetamido-(*p*-nitro[α-^{14}C]benzyl)malonate (I; R = NO_2, R′ = Et), readily isolated from the crude product by recrystallisation from ethyl methyl ketone. In experiments with unlabelled material the yield at this stage was 45%, nitration probably also occurring in the 2-position. In the ^{14}C-synthesis, the 4-nitro-compound remaining in the mother-liquors was recovered by dilution with unlabelled 4-nitro-ester. [Although there is a serious drop in yield at this stage, alternative routes to the nitro- or corresponding amino-compound were less satisfactory. *p*-Nitro-, *p*-acetamido-, and *p*-phthalimido-benzonitrile were prepared by Sandmeyer reactions with ^{14}C-cyanide, but with a deficiency of the cyanide in place of the conventional excess for economic reasons. Yields (on cyanide) were then low and the products contaminated with highly coloured by-products.] The nitro-compound was converted into the amino-derivative and *p*-di-(2-chloroethyl)amino-DL-phenyl[β-^{14}C]-alanine (IV) by the methods described in Part I adapted to a smaller scale, the final yield from the nitro-compound being 79% and the radioactive yield from carbon dioxide 22%.

Experimental

N-Acetyl-p-*nitro*-DL-, -L- *and* -D-*phenylalanine* (II; R = NO_2, R′ = H).—Diethyl α-acetamido-α-*p*-nitrobenzylmalonate (50 g.) was refluxed for 24 hr. with sodium carbonate (50 g.) in water (500 ml.) (cf. Albertson, *loc. cit.*). To the stirred, hot, filtered solution was slowly added concentrated hydrochloric acid (110 ml.). Solid separated, the solution frothed vigorously, and its temperature rose. The mixture was boiled with stirring for a few minutes, cooled, and left at 0° overnight. The pale brown crystalline product (28 g., 78%) was filtered off and had m. p 205—209°. Recrystallisation from water (charcoal) gave colourless needles of *N-acetyl-p-nitro*-DL-*phenylalanine*, m. p. 207—209° (Found: C, 52·7; H, 5·0; N, 10·7. $C_{11}H_{12}O_5N_2$ requires C, 52·4; H, 4·8; N, 11·1%).

To a solution of the DL-acid (23·55 g.) in hot ethanol (200 ml.) was added one of brucine (36·9 g., 1·00 mol.) in hot ethanol (200 ml.), and the mixture left overnight at room temperature. Pale yellow prisms were deposited. The mixture was cooled in ice-water for 1 hr., and the product, m. p. 203—208° (25·35 g., 0·42 mol.) filtered off. Recrystallisation from ethanol gave pale yellow prisms of the *brucine salt*, m. p. 207—209·5°, $[\alpha]_D^{21}$ +19·2° ± 0·5° (*c*, 1·59 in 1 : 1 H_2O–dioxan), of *N*-acetyl-*p*-nitro-L-phenylalanine. Recrystallisation did not significantly affect the rotation or m. p. (Found: C, 61·1; H, 5·85; N, 8·6. $C_{34}H_{38}O_9N_4,H_2O$ requires C, 61·0; H, 6·0; N, 8·4. Found, after drying at 100°/1 mm. for 4 hr.: C, 62·7; H, 6·2; N, 8·6. $C_{34}H_{38}O_9N_4$ requires C, 63·1; H, 5·9; N, 8·7%).

Treatment of an aqueous solution of the salt with ammonia or sodium hydroxide, removal of the brucine by filtration, acidification of the filtrate, and recrystallisation of the product from water yielded colourless prisms of *N-acetyl*-p-*nitro*-L-*phenylalanine*, initial m. p. 170—172°, resolidification, final m. p. 206—209°, $[\alpha]_D^{24}$ +49·7° ± 1° (*c*, 1·55 in EtOH) (Found: C, 52·5; H, 4·8; N, 11·0. $C_{11}H_{12}O_5N_2$ requires C, 52·4; H, 4·8; N, 11·1%).

The ethanolic mother-liquors from the brucine salt were evaporated to dryness under a vacuum, and the residual gum was taken up in hot water. Crystallisation set in on cooling. After an hour at 0°, the product (36·95 g.) was collected and recrystallised from water, yielding yellow prisms of the *brucine salt pentahydrate*, m. p. 98—99°, $[\alpha]_D^{21}$ −36·9° ± 0·5° (*c*, 1·63 in 1 : 1 H_2O–dioxan), of *N*-acetyl-*p*-nitro-D-phenylalanine. Recrystallisation raised the $[\alpha]_D^{21}$ to −37·6° ± 0·5° (*c*, 1·60) (Found, on a sample dried in a vacuum-desiccator over H_2SO_4: C, 55·3; H, 6·6; N, 7·9. $C_{34}H_{38}O_9N_4,5H_2O$ requires C, 55·4; H, 6·6; N, 7·6. Found, on a sample dried to constant wt. at 80° in a high vacuum: C, 62·8; H, 5·65; N, 9·0. $C_{34}H_{38}O_9N_4$ requires C, 63·1; H, 5·9; N, 8·7%). Treatment of an aqueous solution of the salt with aqueous ammonia, removal of the precipitated brucine, acidification with hydrochloric acid, and recrystallisation of the product from water gave colourless prisms of *N-acetyl*-p-*nitro*-D-*phenylalanine*, initial m. p. 170—172°, resolidification, final m. p. 205—206°, $[\alpha]_D^{23}$ −44° ± 0·5° (*c*, 1·45 in EtOH) (Found: C, 52·3; H, 4·8; N, 11·2%).

N-Acetyl-p-*nitro*-L- *and* -D-*phenylalanine Ethyl Ester* (II; R = NO_2, R′ = Et).—(*a*) *p*-Nitro-L-phenylalanine ethyl ester hydrochloride (2·0 g.) prepared from L-phenylalanine (Bergel and Stock, *loc. cit.*) was acetylated in 75% yield by 10 minutes' heating with acetic anhydride–potassium carbonate. Crystallisation of the product from water gave colourless needles of the L-*acetyl compound*, m. p. 115—117°, $[\alpha]_D^{19}$ +13·5° ± 0·5° (*c*, 1·32 in EtOH) (Found: C, 55·9; H, 5·8; N, 10·2. $C_{13}H_{16}O_5N_2$ requires C, 55·7; H, 5·75; N, 10·0%).

(*b*) *N*-Acetyl-*p*-nitro-L-phenylalanine (70 mg.) from the brucine salt was esterified with 2N-ethanolic hydrogen chloride (2 days at room temperature). Evaporation of the solvent gave a colourless gum which crystallised from water in tiny colourless needles (90%) of the L-acetyl compound, m. p. 115—117°, unchanged on admixture with product obtained as in (*a*); the $[\alpha]_D^{19}$ +13·0° ± 0·5° (*c*, 1·33 in EtOH) established that the compound belonged to the L-series.

The D-ester was obtained similarly in comparable yield from the D-acid. Recrystallisation from water gave a *product* of m. p. 116—118°, $[\alpha]_D^{22}$ −11·0° ± 1·0° (*c*, 1·58 in EtOH) (Found: C, 55·9; H, 5·5; N, 9·9%).

N^{α}-*Acetyl*-p-*amino*-DL-, -L-, *and* -D-*phenylalanine Ethyl Ester* (II; R = NH_2, R′ = Et).—(*a*) Diethyl acetamido-4-aminobenzylmalonate (2·75 g.) was refluxed for 4 hr. with 2·65N-sodium hydroxide (14 ml.), and the solution acidified with 3·06N-hydrochloric acid (12·2 ml.) and refluxed for 1 hr. (cf. Snyder *et al.*, *loc. cit.*). Evaporation *in vacuo*, extraction with ethanol, and evaporation of the solvent gave a gum which was kept in 3N-ethanolic hydrogen chloride (10 ml.) at room temperature for 3 days. Treatment of an aqueous solution of the product with ammonia, extraction into ethyl acetate, and crystallisation from benzene or water gave colourless prisms of the *ester*, m. p. 107—108°, raised to 109—110° on recrystallisation from benzene (Found: C, 62·2; H, 7·30; N, 11·3. $C_{13}H_{18}O_3N_2$ requires C, 62·4; H, 7·25; N, 11·2%). The *picrate* crystallised from benzene–ethanol in yellow needles, m. p. 161—162° (Found: N, 14·7. $C_{19}H_{21}O_{10}N_5$ requires N, 14·6%).

(*b*) *N*-Acetyl-*p*-nitro-L-phenylalanine ethyl ester (0·56 g.) was completely hydrogenated in methanol over 1% palladium–calcium carbonate (0·2 g.) in 15 min. The product was a gum. A little of the amine was heated on a steam-bath for 20 min. with a molar equivalent of 2 : 4-dinitrofluorobenzene. The N^{α}-*acetyl*-p-(2 : 4-*dinitrophenyl*)*amino*-L-*phenylalanine ethyl ester* crystallised from ethanol in tiny yellow needles, m. p. 153—156°, $[\alpha]_D^{23}$ +54° ± 1° (*c*, 0·86 in dioxan) (Found: C, 54·6; H, 4·7; N, 13·3. $C_{19}H_{20}O_7N_4$ requires C, 54·8; H, 4·8; N, 13·5%).

N^{α}-Acetyl-*p*-amino-D-phenylalanine ethyl ester was obtained similarly as a gum which gave

a 2 : 4-*dinitrophenyl*-D-*derivative*, m. p. 155—159°, $[\alpha]_D^{22}$ −54·5° ± 1·0° (*c*, 0·88 in dioxan) (Found : C, 55·0; H, 4·7; N, 13·1%).

The DL-amine (1·50 g., 0·006 mole) and ammonium α-bromocamphor-π-sulphonate (0·987 g., 0·003 mole) were dissolved in warm methanol (10 ml.), and N-hydrochloric acid (3 ml.) was added. The solution was taken to dryness (water-pump; steam-bath), then to dryness with methanol. The residue crystallised from methanol in colourless prisms (1·685 g.). Two further crystallisations from methanol gave the *bromocamphorsulphonate*, m. p. 236—238° (decomp.), $[\alpha]_D^{21}$ +53° ± 1° (*c*, 0·94 in H_2O), of N^{α}-acetyl-*p*-aminophenylalanine ethyl ester (Found : C, 49·4; H, 6·1; N, 5·1. $C_{22}H_{33}O_7N_2BrS$ requires C, 49·2; H, 5·9; N, 5·0%). Treatment of the aqueous solution of this salt with ammonia extraction with ethyl acetate, evaporation of the solvent, and crystallisation of the residue from benzene yielded the free base (73%), m. p. 109—111°, of negligible optical activity.

N^{α}-*Acetyl*-p-N-*o*′-*carboxybenzamido*-DL-*phenylalanine Ethyl Ester* (II ; R = *o*-$HO_2C{\cdot}C_6H_4{\cdot}CO{\cdot}NH$, R′ = Et).—$N^{\alpha}$-Acetyl-*p*-amino-DL-phenylalanine ethyl ester (0·84 g.) and phthalic anhydride (0·50 g., 1·00 mol.) were refluxed for 15 min. in ethyl acetate (10 ml.). The solid remaining after evaporation crystallised from ethanol in colourless needles (97%) of the monosolvated *carboxybenzoyl compound*, m. p. 177—179° (Found : C, 62·15; H, 6·3; N, 6·5. $C_{21}H_{22}O_6N_2$,EtOH requires C, 62·15; H, 6·35; N, 6·3%).

The sodium salt of the carboxybenzoyl compound and brucine hydrochloride formed a *salt* from water. Recrystallisation from water usually gave a product melting over a range, but the best crystals obtained had m. p. 131—132° (Found, on sample dried at 100° in a high vacuum : C, 63·85; H, 6·0; N, 6·75. $C_{21}H_{22}O_6N_2,C_{23}H_{26}O_4N_2,2H_2O$ requires C, 63·75; H, 6·3; N, 6·8%).

The salt (*ca.* 50 mg.) was dissolved in warm 2N-hydrochloric acid, and the solution cooled and set aside overnight. The colourless prisms formed were recrystallised from water. They were clearly phthalic acid since they contained no nitrogen (sodium fusion test), gave the fluorescein reaction with resorcinol and concentrated sulphuric acid, and had m. p. 204—205°, mixed m. p. with phthalic acid (of m. p. 207—210°) 205—207°.

Hydroxyethylation of N^{α}-*Acetyl*-p-*amino*-DL-, -L-, *and* -D-*phenylalanine Ethyl Ester*.—To a solution of the DL-amine (2·0 g.) in 2N-aqueous acetic acid (16 ml.), ethylene oxide (4 ml.) was added (cf. Everett, Roberts, and Ross, *J.*, 1953, 2386). The mixture was set aside for 24 hr., and then evaporated to dryness under a vacuum. The product was a gum.

Similarly, the gummy L-amine gave a good yield of N^{α}-*acetyl*-p-*di*-(2-*hydroxyethyl*)*amino*-L-*phenylalanine ethyl ester*, which, after two crystallisations from chloroform formed colourless prisms, m. p. 142—144°, $[\alpha]_D^{25}$ +43° ± 1° (*c*, 1·76 in EtOH) (Found : C, 60·0; H, 7·5; N, 8·2. $C_{17}H_{26}O_5N_2$ requires C, 60·3; H, 7·7; N, 8·3%). The D-amine gave, in the same way, the corresponding D-*di*-(2-*hydroxyethyl*)*amino-compound*, m. p. 140—142°, $[\alpha]_D^{24}$ −35° ± 1° (*c*, 1·65 in EtOH) increased to −36° ± 1° by a further crystallisation (Found : C, 60·4; H, 7·4; N, 8·2%).

Chlorination and Hydrolysis of N^{α}-*Acetyl*-p-*di*-(2-*hydroxyethyl*)*amino*-L-, -D-, *and* -DL-*phenylalanine Ethyl Ester*.—(*a*) The DL-compound (362 mg. of gum) was refluxed for 15 min. with dry benzene (5 ml.) and freshly distilled phosphorus oxychloride (1·0 ml.). Two phases were present throughout. The mixture was evaporated to dryness (water-pump) and the residue heated with concentrated hydrochloric acid (5 ml.) for 4 hr. Evaporation to small bulk and addition of concentrated sodium acetate solution to the residual solution gave a near-white precipitate which crystallised from methanol (charcoal) in colourless crystals of *p*-di-(2-chloroethyl)amino-DL-phenylalanine (51%), m. p. and mixed m. p. 181—182° (decomp.).

In another experiment the hydroxyethylated product from the DL-amine (0·3 g.) was refluxed for 15 min. with dry chloroform (5 ml.) and phosphorus oxychloride (1·5 ml.). The mixture became homogeneous after 10 minutes' heating. Evaporation to dryness under a vacuum, refluxing the residue with 6N-hydrochloric acid, evaporation to small bulk, and addition of sodium acetate solution yielded a product which, after crystallisation from methanol, gave the di-(2-chloroethyl)amino-DL-compound, m. p. 179—181° (decomp.), in 12% yield.

N^{α}-Acetyl-*p*-di-(2-hydroxyethyl)amino-L-phenylalanine ethyl ester was chlorinated in the same way in benzene and chloroform severally. In each case, the final product was the racemic chloro-compound.

(*b*) N^{α}-Acetyl-*p*-di-(2-hydroxyethyl)amino-L-phenylalanine ethyl ester (0·45 g.) was refluxed for 4 min. with purified thionyl chloride (1·0 ml.) in dry chloroform (5·0 ml.). The dark solution was taken to dryness (vacuum) and refluxed for 2 hr. with 6N-hydrochloric acid (6 ml.). After 12 hr. the solution was concentrated to small volume. Precipitation by means of sodium

acetate and crystallisation of the dried product from methanol (charcoal) gave almost colourless *p*-di-(2-chloroethyl)aminophenylalanine (55 mg.), m. p. 182—185° (decomp.), $[\alpha]_D^{23}$ −19·5° ± 1·0° (*c*, 0·67 in MeOH) as against $[\alpha]_D^{22}$ −31·5° ± 0·5° (*c*, 0·67) for the compound prepared from L-phenylalanine (Bergel and Stock, *loc. cit.*). A second crop (40 mg.) had m. p. 182—184° (decomp.).

(*c*) The L-dihydroxy-compound (1·0 g.) in dry chloroform (10 ml.) was added with ice-cooling to powdered phosphorus pentachloride (1·25 g.) in dry chloroform (10 ml.), then allowed to warm to room temperature and to stand for 4 hr. with occasional gentle warming for a few seconds on a water-bath. The solvent was evaporated and ice-water poured into the residue. The orange resin was slowly transformed into a pale brown oil. Extraction into chloroform, washing with water, drying ($MgSO_4$), evaporation of the solvent, dissolution in benzene, and finally passage through a short alumina column with benzene and then chloroform for elution gave a pale yellow gum (0·55 g.) which had a very approximate $[\alpha]_D^{23}$ of +29° (*c*, 2·75 in $CHCl_3$). The gum was refluxed for 2·5 hr. with 6N-hydrochloric acid (10 ml.), and the product isolated in the normal way with sodium acetate. Crystallisation from methanol gave a first crop (0·120 g.) of *p*-di-(2-chloroethyl)aminophenylalanine, m. p. 183—185° (decomp.), unchanged on admixture with authentic DL-compound. The product had no detectable optical activity (*c*, 0·67 in MeOH).

p-*Nitro*-L- *and* -D-*phenylalanine Ethyl Ester Hydrochloride.*—*N*-Acetyl-*p*-nitro-L-phenylalanine (0·5 g.; $[\alpha]_D^{24}$ +50°) was refluxed for 2·5 hr. with 6N-hydrochloric acid (10 ml.). The solution was evaporated to dryness (vacuum), and the crystalline residue evaporated with ethanol (vacuum), and then refluxed for 1·5 hr. with 2N-ethanolic hydrogen chloride (8 ml.). Evaporation of the solvent and crystallisation of the residue from acetone–methanol gave the L-ester hydrochloride (0·440 g.), m. p. 203—205° (decomp.), unchanged on admixture with the L-compound, m. p. 204—205° (decomp.), prepared from *p*-nitro-L-phenylalanine (Bergel and Stock, *loc. cit.*), $[\alpha]_D^{20}$ +11·7° ± 0·5° (*c*, 2·3 in H_2O).

The D-ethyl ester hydrochloride was prepared in the same way from *N*-acetyl-*p*-nitro-D-phenylalanine ($[\alpha]_D^{22}$ −39°). It had m. p. 208—209° (mixed m. p. 205—206° with authentic specimen of m. p. 204—205°) and $[\alpha]_D^{22}$ −10·3° ± 0·5° (*c*, 2·2 in H_2O).

Diethyl p-*Nitrobenzylphthalimidomalonate* (III; R = NO_2, R′ = Et, R″ = CO_2Et).—Diethyl sodiophthalimidomalonate (Barger and Weichselbaum, *loc. cit.*) (6·52 g.) was dissolved in boiling ethyl methyl ketone (80 ml.), and a solution of *p*-nitrobenzyl chloride (3·44 g., 1·0 mol.) in the same solvent (20 ml.) was added. Sodium iodide (*ca.* 0·5 g.), dissolved in hot ketone (10 ml.), was introduced, and produced immediate precipitation. The mixture was refluxed for 1·5 hr., cooled, filtered, and evaporated under a vacuum and the residual gum crystallised from ethanol. The *malonate* formed colourless prisms (88%), m. p. 103—105°, sharpening to 104—105° on recrystallisation from ethanol (Found: C, 59·8; H, 4·5; N, 6·4. $C_{22}H_{20}O_8N_2$ requires C, 60·0; H, 4·6; N, 6·4%).

N-Carboxybenzoyl-p-*nitro*-DL-*phenylalanine* (cf. Albertson, *loc. cit.*).—Diethyl *p*-nitrobenzylphthalimidomalonate (70 g.) and sodium carbonate (70 g.) in water (700 ml.) were refluxed overnight with stirring (to avoid bumping). The clear brown solution was acidified with hydrochloric acid, and refluxing and stirring were continued for a further 40 min. The mixture was cooled and the colourless precipitate (31 g.) collected. A second crop (18·5 g.) was obtained on evaporation of the mother-liquors. Crystallisation from aqueous ethanol gave the *compound* as small needles, m. p. 198—200° (Found, in sample dried at 100° in a high vacuum: C, 56·8; H, 4·1; N, 7·8. $C_{17}H_{14}O_7N_2$ requires C, 57·0; H, 3·9; N, 7·8%).

Ring-closure to the Acid (III; R = NO_2, R′ = R″ = H).—The *N*-carboxybenzoyl compound (2·7 g.) was refluxed for 30 min. with acetic anhydride (10 ml.), the mixture taken to dryness (vacuum), and the residue heated with water. The cooled gummy product became granular when rubbed and crystallised from ethyl methyl ketone–light petroleum or aqueous ethanol in almost colourless needles, m. p. 184—186°, of *p*-nitro-*N*-phthaloyl-DL-phenylalanine.

The same compound, prepared from *p*-nitrophenylalanine and phthalic anhydride and reported in Part I as having m. p. 180—181°, had m. p. 185—186° after recrystallisation from aqueous ethanol, unchanged on admixture with the foregoing material.

Resolution. Solutions of *p*-nitro-*N*-phthaloyl-DL-phenylalanine (1·0 g.) in methanol (25 ml.) and of cinchonidine (0·865 g., 1·00 mol.) in methanol (30 ml.) were mixed. Crystallisation soon set in. The mixture was left overnight, and the colourless needles (0·97 g.), m. p. 209—210°, were collected. After two recrystallisations from methanol the *cinchonidine salt* of the D-acid had m. p. 211° and $[\alpha]_D^{21}$ +82° ± 1° (*c*, 0·84 in dioxan) (Found, after drying at 100° in a high vacuum: C, 67·0; H, 5·8; N, 8·8. $C_{35}H_{34}O_7N_4$,MeOH requires C, 66·7; H, 5·7; N, 8·4%).

To the salt (2·9 g.) in warm ethanol (50 ml.) was added water (50 ml.) and a slight excess (*ca.* 10 ml.) of N-aqueous sodium hydroxide. The mixture was diluted with water, cooled, and filtered from the precipitated base, and the filtrate acidified with hydrochloric acid. The tiny needles of *p-nitro*-N-*phthaloyl*-D-*phenylalanine* (1·05 g.) had, after recrystallisation from ethanol, m. p. 207—208°, $[\alpha]_D^{20}$ +240° ± 2° (*c*, 1·01 in EtOH) (Found: C, 60·1; H, 3·7; N, 8·2. $C_{17}H_{12}O_6N_2$ requires C, 60·0; H, 3·55; N, 8·2%). Refluxing with 2N-ethanolic hydrogen chloride yielded *p*-nitro-*N*-phthaloyl-D-phenylalanine ethyl ester, m. p. 82—83°, $[\alpha]_D^{20}$ +206° ± 1° (cf. Part I).

Evaporation of the mother-liquors from the original cinchonidine experiment gave a gum which crystallised readily from aqueous ethanol in almost colourless needles (0·73 g.), m. p. 191—192·5°. Two recrystallisations from aqueous ethanol gave the L-acid cinchonidine *salt*, m. p. 192·5—194°, $[\alpha]_D^{20}$ −170° ± 1° (*c*, 1·32 in EtOH) (Found, after drying at 100° in a high vacuum: C, 66·2; H, 5·6; N, 8·6. $C_{36}H_{34}O_7N_4,H_2O$ requires C, 66·3; H, 5·5; N, 8·6%).

The acid was isolated as for the D-isomer. The recrystallised *p-nitro*-N-*phthaloyl*-L-*phenylalanine* had m. p. 209—211° and $[\alpha]_D^{21}$ −233° ± 2° (Found: C, 60·3; H, 3·8; N, 8·4%).

Conversion into the L-ethyl ester gave, after two recrystallisations, a product of m. p. and mixed m. p. 84—85°, $[\alpha]_D^{20}$ −212° ± 2° (cf. Part I).

[α-^{14}C]*Benzyl Chloride.*—[*carboxy*-^{14}C]Benzoic acid was obtained (89% yield) by treating the carbon dioxide from $Ba^{14}CO_3$ (8 mc, 4·0 millimoles) with an approximately M-solution of phenylmagnesium bromide (6 ml.) at −60° and proceding in the usual way (Calvin, *loc. cit.*).

This material was reduced (10 ml. of 5% lithium aluminium hydride in ether) and the crude benzyl alcohol obtained was treated overnight with a solution (2 ml.) of anhydrous zinc chloride (7 g.) in concentrated hydrochloric acid (5 ml.). The benzyl chloride was extracted with light petroleum (b. p. 80—100°), washed with sodium hydrogen carbonate solution, and filtered through anhydrous sodium sulphate. The solution was used directly for the next stage.

Diethyl Acetamido-([α-^{14}C]*benzyl*)*malonate.*—Thebenzyl chloride solution was added to diethyl acetamidomalonate (1·09 g.) dissolved in N-sodium ethoxide (5 ml.) and ethanol (10 ml.) and held for 6 hr. at 75—80°. The solvent was then evaporated and the residue extracted with chloroform. The filtered (charcoal) solution was evaporated to small bulk and crystallised by addition of light petroleum (yield, 827 mg., 67% from CO_2).

DL-[β-^{14}C]*Phenylalanine.*—Diethyl acetamido-([α-^{14}C]benzyl)malonate (216 mg.) was refluxed for 5 hr. with constant-boiling hydrochloric acid (1 ml.). Evaporation, dissolution in water, and precipitation with ammonia gave the crude phenylalanine, which was recrystallised from water. The yield was 81 mg. (70%), and the specific activity 1·96 mc/millimole. The compound showed the same R_F value as DL-phenylalanine when run on buffered paper with 1 : 1 benzyl–butyl alcohol (McFarren, *Analyt. Chem.*, 1951, **23**, 168).

Nitration of Diethyl Acetamidobenzylmalonate.—(*a*) To a solution of diethyl acetamidobenzylmalonate (1·54 g.) in acetic anhydride (4·0 ml.), cooled to 0°, fuming nitric acid (1·0 ml.) was added with stirring during 15 min. The mixture was set aside at room temperature for 2 hr. It deposited a few crystals. Ice and water (12 g.) were added; a precipitate was formed which when dry weighed 1·61 g. Two crystallisations from ethyl methyl ketone gave 0·78 g. (45%) of diethyl acetamido-*p*-nitrobenzylmalonate, m. p. and mixed m. p. 192—194° (cf. Elliott and Harington, *J.*, 1949, 1374) (Found: C, 54·6; H, 5·8; N, 7·9. Calc. for $C_{16}H_{20}O_7N_2$: C, 54·5; H, 5·7; N, 8·0%).

(*b*) To diethyl acetamido-([α-^{14}C]benzyl)malonate (611 mg.) in acetic anhydride (1·6 ml.) was added fuming nitric acid (0·40 ml.) at 0°, and the product was worked up as in (*a*), to give the ^{14}C-nitro-compound (231 mg.). Pure (unlabelled) nitro-compound (231 mg.) was recrystallised from the mother-liquors, giving a further amount of diluted ^{14}C-compound (227 mg.).

*Diethyl Acetamido-*p-*amino*([α-^{14}C]*benzyl*)*malonate.*—The ^{14}C-nitro-compound (458 mg.) obtained as in (*b*) above was suspended in ethyl acetate (10 ml.) and reduced in the presence of palladium–barium carbonate, and the product recrystallised from ethyl acetate–light petroleum (yield 368 mg., 87%).

p-*Di*-(2-*chloroethyl*)*amino*-DL-*phenyl*[β-^{14}C]*alanine.*—To the amino-compound (368 mg.) in glacial acetic acid (1 ml.) was added a 20% solution of ethylene oxide in water (3 ml.). After 24 hr., water (10 ml.) was added and the solution neutralised by solid sodium hydrogen carbonate (*ca.* 2 g.). The precipitate was extracted with chloroform (3 × 5 ml.), and the extract filtered through anhydrous sodium sulphate, and finally dried by boiling down to about half its volume. The solution was gently refluxed for 10 min. with thionyl chloride (0·5 ml.). Concentrated hydrochloric acid (5 ml.) was immediately added, and the mixture refluxed for 3 hr. under an air condenser, the chloroform being allowed to evaporate. After evaporation to

dryness *in vacuo*, the residue was dissolved in water (5 ml.) and decolorised with charcoal, and the product precipitated by the addition of sodium acetate solution. The product (315 mg., 89%) was obtained as a pale cream powder, and stored in this condition for recrystallisation before use. The specific activity was 1·28 mc/millimole, the radioactive yield from CO_2 22%, the m. p. 177—178°, and the mixed m. p. 179—180° (Found : Cl, 23·4. Calc. for $C_{13}H_{18}O_2N_2Cl_2$: Cl, 23·3%).

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Heats of Mixing of Liquids.

By Joyce Canning and G. H. Cheesman.

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Heats of mixing of some substituted benzenes have been measured.

This work is a continuation of that of Cheesman and Whitaker (*Proc. Roy. Soc.*, 1952, *A*, **212**, 406). Measurements with the same calorimeter have been made at 24·33° of the heats of mixing of the six combinations in pairs of benzene, toluene, chlorobenzene, and bromobenzene. Several of these pairs have been reported as ideal on the basis of liquid–vapour equilibrium measurements, but this merely means that the measurements were too crude to detect deviations from ideality (Guggenheim, *Trans. Faraday Soc.*, 1937, **33**, 151). For all these mixtures the heat of mixing per mole was expected and found to be small compared with RT.

Experimental

The experimental procedure followed closely that described by Cheesman and Whitaker (*loc. cit.*), using a small copper vessel in which the two liquids were separated by a tinfoil diaphragm. This diaphragm was broken at the moment of mixing by a steel armature which also acted as a magnetic stirrer. The vessel was supported in an evacuated housing in a thermostat, and the temperature difference between the calorimeter and the surrounding bath was recorded by copper–constantan thermojunctions connected to a galvanometer.

The cylinder consisted of two vessels; one was fixed permanently to its supports and carried the calibrating winding and thermocouple. The second vessel, which screwed on to the first and clamped the breakable diaphragm, carried a glass capillary in which an air bubble served to cushion any change of volume. Several interchangeable vessels of this type (" caps ") having different capacities enabled different molar ratios of mixing to be attained.

The course of each experiment was similar to that described by Cheesman and Whitaker, but whereas all the pairs of liquids previously studied mixed endothermically, three of the six new mixtures were found to mix exothermically. Consequently the plot of the galvanometer scale reading against time was of a different shape. Examples of such plots are shown in Fig. 1*a* for a typical endothermic mixture and in Fig. 1*b* for a typical exothermic mixture. In both cases the essential assumption is that the ratio of the enthalpy increase of mixing (ΔH) to the input of electrical energy (VIt) during the calibration period is equal to the ratio of FA to CG where F and G are determined by extrapolation of CB and of ED respectively. Owing to induction effects, galvanometer readings could not be taken during operation of the magnetic stirrer, and extrapolation was necessary during this period.

Initially it was found that the reproducibility of the results on the system bromobenzene–toluene was much worse than expected. This was due to inadequate mixing, probably owing to the widely differing densities of the two components. Thereafter the rate of stirring was doubled, and a correction applied for the temperature increase produced by the stirring. This

correction was found to be constant for each cap and in each case equivalent to a galvanometer deflection of less than 1 mm. Corrections were applied to all results for the mixtures chlorobenzene–bromobenzene, bromobenzene–toluene, and bromobenzene–benzene. The variation in ΔH produced by including this correction decreases as ΔH increases, and is much smaller for exothermic than for endothermic mixtures since in the former case both FA and CG are increased, whilst in the latter case FA is decreased and CG increased in magnitude. The maximum change in the value of ΔH occasioned by this correction is 2% for the mixture bromobenzene–toluene, 10% for chlorobenzene–bromobenzene, and about 15% for bromobenzene–benzene. The volume change on mixing was too small in every case to be measured by observation of movement of the meniscus in the capillary tube.

FIG. 1*a*.

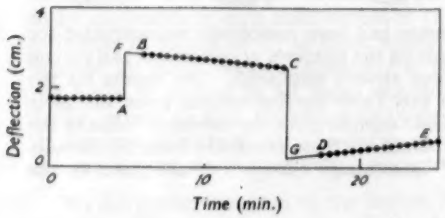


FIG. 1*b*.

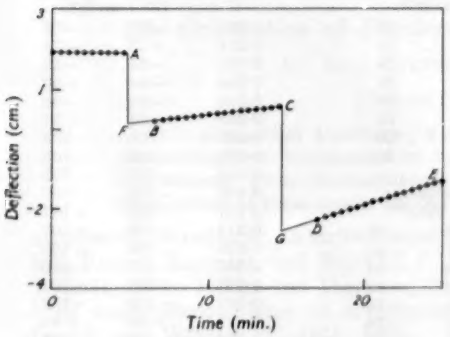
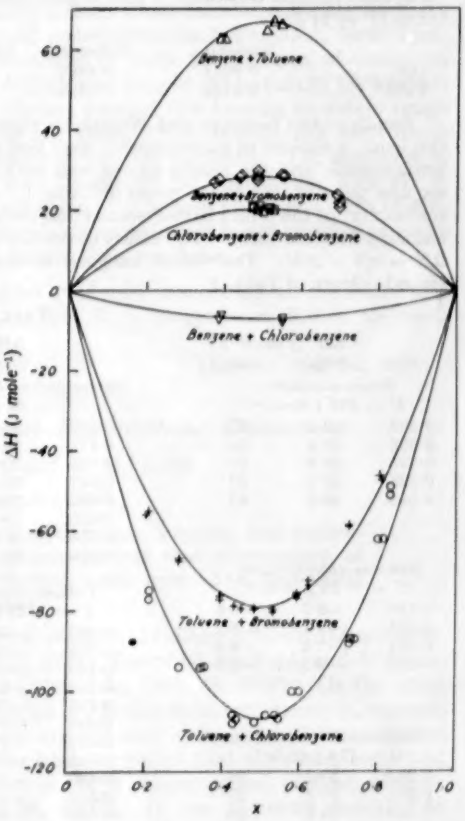


FIG. 2.



Materials.—All distillations were carried out in a fractionating column having an efficiency of 27 theoretical plates and a reflux ratio of 10 : 1.

Benzene. B.D.H. crystallisable benzene was shaken with concentrated sulphuric acid (4 times), water, 10% sodium carbonate solution and water successively. It was then distilled once and fractionally crystallised.

Toluene. Two batches were used. The first was purified by shaking a good commercial product with Raney nickel followed by drying it over sodium and distillation twice. It was then fractionally crystallised five times. Since this toluene had an unexpectedly low density we also made measurements with a sample of specially purified toluene kindly supplied to us by Dr. Tompa at Courtaulds' Research Laboratories. This had been prepared by distillation of the commercial product through a 100-plate column packed with 1/16" gauge Dixon rings, with

a reflux ratio of 100 : 1. Our toluene was used in the measurements on mixtures with chlorobenzene and with bromobenzene; when Dr. Tompa's material was received some of these measurements were repeated but the heats of mixing were not significantly different. Dr. Tompa's material was used for all the measurements here reported of mixtures of benzene and toluene, as the low-density material gave an appreciably higher heat of mixing.

Bromobenzene. B.D.H. bromobenzene was fractionally distilled once and dried (P_2O_5).

Chlorobenzene. B.D.H. chlorobenzene was dried ($CaCl_2$) and distilled once.

A comparison of the densities of the purified liquids with published values (Timmermans, "Physico-chemical constants of pure organic compounds," Elsevier, Amsterdam, 1950) is given below ($T = 24{\cdot}33°$).

	Benzene	Toluene	Toluene (Tompa)	Bromobenzene	Chlorobenzene
Obs.	0·8743	0·8592	0·8626	1·4892	1·1015
Publ.	0·8744	0·8628	0·8628	1·4889	1·1018

Results.—As Cheesman and Whitaker's calorimeter had been completely reconstructed for this work, a number of measurements were first made on the mixtures of chloroform and carbon tetrachloride, and the results agreed well with those already published. The results for the six new pairs of liquids are given in Table 1. In this Table the first column gives the mole fraction (x) of the liquid named second and the second column gives the measured value of the enthalpy increase (ΔH). The values in the third column are those calculated from the formula $\Delta H = x(1 - x)U$. The values assigned to the "interchange energy" U are given in the second column of Table 2.

TABLE 1.

x	ΔH (j mole^{-1}) (exp.)	(calc.)
Benzene–toluene; U = 268 j mole^{-1}.		
0·385	62·4	63
0·396	62·4	64
0·505	64·8	67
0·524	67·1	67
0·542	66·3	67
Benzene–chlorobenzene; U = − 28 j mole^{-1}.		
0·386	−6·5	−6·6
0·391	−6·1	−6·7
0·551	−7·2	−6·9
0·552	−6·9	−6·9
Benzene–bromobenzene, U = 114 j mole^{-1}.		
0·374	27·0	27
0·385	27·8	27
0·440	28·3	28
0·442	28·7	28
0·484	27·7	28
0·486	29·9	28
0·486	28·3	28
0·549	29·1	28
0·552	28·9	28
0·690	23·9	24
0·694	21·0	24
0·695	21·9	24

x	ΔH (j mole^{-1}) (exp.)	(calc.)
Chlorobenzene–bromobenzene; U = 82 j mole^{-1}.		
0·472	21·2	20
0·473	20·8	20
0·486	20·3	20
0·487	20·3	20
0·490	21·2	20
0·500	19·8	20
0·514	20·6	20
0·526	20·3	20
Toluene–bromobenzene; U = − 316 j mole^{-1}.		
0·200	−55·8	−51
0·205	−55·1	−52
0·284	−67·6	−64
0·286	−67·2	−65
0·393	−76·4	−76
0·393	−77·2	−76
0·428	−78·9	−77
0·445	−79·6	−78
0·480	−79·5	−79
0·529	−80·2	−79
0·530	−79·8	−79
0·589	−76·3	−77
0·589	−76·5	−77
0·591	−75·9	−76
0·619	−73·4	−75
0·619	−72·6	−75
0·725	−58·6	−63
0·726	−59·1	−63
0·805	−46·6	−50
0·808	−47·5	−49

x	ΔH (j mole^{-1}) (exp.)	(calc.)
Toluene–chlorobenzene; U = − 428 j mole^{-1}.		
0·209	−75	−71
0·211	−77	−71
0·291	−94	−88
0·298	−94	−90
0·301	−94	−90
0·304	−94	−91
0·430	−108	−105
0·431	−106	−105
0·434	−107	−105
0·486	−108	−107
0·487	−108	−107
0·512	−106	−107
0·538	−106	−106
0·546	−107	−106
0·582	−100	−104
0·600	−100	−103
0·727	−88	−85
0·730	−87	−84
0·732	−87	−84
0·741	−87	−82
0·800	−62	−68
0·812	−62	−65
0·832	−49	−60
0·832	−51	−60

TABLE 2.

Mixture	U (j mole^{-1}) (exp.)	(Hildebrand)	Mixture	U (j mole^{-1}) (exp.)	(Hildebrand)
Benzene–toluene	268	29	Chlorobenzene–bromobenzene...	82	17
Benzene–chlorobenzene	−28	49	Toluene–bromobenzene	−316	71
Benzene–bromobenzene	114	9	Toluene–chlorobenzene	−428	159

DISCUSSION

All the measurements and the calculated parabolic curves are shown in Fig. 2. For the two most exothermic mixtures (toluene–chlorobenzene and toluene–bromobenzene) the deviations between the experimental points and the parabolæ seem to be systematic. These deviations are however neither large enough nor sufficiently firmly established to warrant more detailed analysis at this stage. The formulæ used for calculating ΔH are probably not accurate to within ± 5 joules mole^{-1}; the maximum observed deviation does not exceed twice this value and for the majority of the experimental points it is much less.

A comparison of the experimental values of U with those calculated by Hildebrand's (cf. Hildebrand and Scott, "The solubility of non-electrolytes," Reinhold, New York, 1950) well-known formula is given in the 3rd column of Table 2. There is, of course, no correlation. It is only fair to mention that Hildebrand himself did not claim his formula to be applicable to such small values of U. He put forward this formula to obtain rough estimates of values of U, in cases where it is not small. The formula has been much misused by many workers, especially in the field of polymer solutions. The smallness of the heats of mixing in all these mixtures may be gauged by comparison with $RT \simeq 2{\cdot}5$ kJ mole^{-1}, so that the numerically greatest value of U is only about one sixth of RT. In the present state of our knowledge of molecular interactions it is not possible to make any predictions about such values except to foresee their smallness.

We are greatly indebted to the British Rubber Producers' Association for the award of a research scholarship to one of us (J. C.), and to Prof. E. A. Guggenheim, F.R.S., for much helpful discussion.

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The Orientation of Disubstituted Fluoranthene Derivatives.

By NEIL CAMPBELL and N. H. KEIR.

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It is shown that 4-carboxy-, 4-methoxycarbonyl-, 4-cyano-, and 4-nitrofluoranthene are brominated in the 12-position and that sulphonation of fluoranthene gives fluoranthene-4 : 12-disulphonic acid. The theoretical implications of these results are discussed.

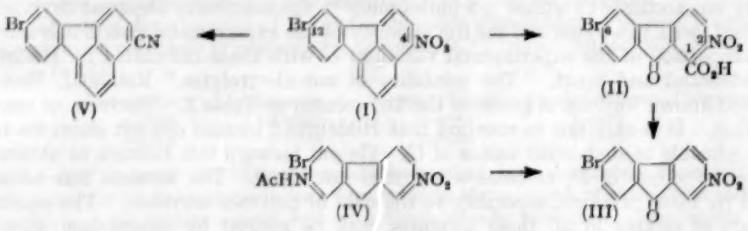
4-BROMOFLUORANTHENE, on further bromination, yields 4 : 11-dibromofluoranthene (Campbell, Easton, Rayment, and Wilshire, *J.*, 1950, 2784; Campbell, Stafford, and Wilshire, *J.*, 1951, 1137; Holbro and Tagmann, *Helv. Chim. Acta*, 1950, **33**, 2178). On the other hand 4-acetylfluoranthene on acetylation yields 4 : 12-diacetylfluoranthene (Campbell, Leadill, and Wilshire, *J.*, 1951, 1404). These are the only disubstituted fluoranthenes which have been rigidly orientated, but it has been suggested that the disulphonic acid obtained by the sulphonation of fluoranthene is the 4 : 11-compound (Tobler, Holbro, Sutter, and Kern, *Helv. Chim. Acta*, 1941, **24**, 100E). It was therefore desirable to orientate other disubstituted fluoranthenes: we have established the structures of five such. The structural proof is rigorous except for the disulphonic acid.

Bromination of 4-nitrofluoranthene in nitrobenzene affords 12-bromo-4-nitrofluoranthene (I) since when reduced, diazotised, and treated with cuprous bromide the latter yields 4 : 12-dibromofluoranthene identical with a sample prepared from 4 : 12-diacetylfluoranthene.

Oxidation of the bromonitrofluoranthene gives 6-bromo-2-nitrofluorenone-1-carboxylic acid (II), which when heated in quinoline yields 2-nitrofluorenone. This loss of bromine in the 6-position is not surprising, since the lability of bromine in the 3-position of fluorenone has been reported (Montagne, *Rec. Trav. chim.*, 1909, **28**, 449). Decarboxylation in pyridine, however, affords 6-bromo-2-nitrofluorenone (III) which was synthesised by brominating 2-acetamido-7-nitrofluorene to give the 3-bromo-derivative (IV). Hydrolysis followed by removal of the amino-group yields 6-bromo-2-nitrofluorene, which is oxidised to 6-bromo-2-nitrofluorenone (III) identical with the substance prepared above. This

series of reactions incidentally proves that bromination of 2-acetamido-7-nitrofluorene occurs at the 3- and not at the 1-position (cf. Bell and Mulholland, *J.*, 1949, 2020).

4-Cyanofluoranthene is likewise brominated in the 12-position since the product (V) was identical with 12-bromo-4-cyanofluoranthene obtained from 4-amino-12-bromofluoranthene. The cyano-compound was converted into 12-bromofluoranthene-4-carboxylic acid and its methyl ester, which were required as reference compounds. They were

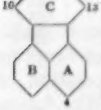


found to be identical with the bromination products of fluoranthene-4-carboxylic acid and its methyl ester, thus showing that substitution had again occurred in the 12-position. The bromination of 4-acetylfluoranthene was attempted, but no pure product was isolated.

Of interest is the orientation of the disulphonic acid obtained by the direct sulphonation of fluoranthene (Goldschmiedt, *Monatsh.*, 1880, **1**, 221; von Braun and Manz, *Annalen*, 1931, **488**, 111; G.P. 575,953) which it has been suggested is the 4 : 11-compound on account of the quinhydrone-type product obtained by fusion with alkali (Tobler *et al.*, *loc. cit.*). Since monosulphonation occurs mainly in the 4-position the disulphonic acid must contain one sulpho-group in that position, and by analogy with the effect of other *m*-directing groups discussed above it is to be expected that the second sulpho-group will occupy the 12-position. Many unsuccessful attempts were made to convert the disulphonic acid into known reference compounds. Success was achieved by fusing the acid with potassium hydroxide to give a dihydroxy-compound, methylation of which yielded a product identical with a specimen prepared from 4 : 12-diacetylfluoranthene (VIII) (Camp-

bell, Leadill, and Wilshire, *loc. cit.*). This diacetylfluoranthene was oxidised by perbenzoic acid (Friess *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 14; 1950, **72**, 5518; 1951, **73**, 3968). The diacetate thus formed was hydrolysed and with diazomethane then gave 4 : 12-dimethoxyfluoranthene identical with the compound mentioned above. Unless therefore the fusion of the sulphonic acid with alkali has been accompanied by the migration of one or both sulpho-groups the acid is indeed fluoranthene-4 : 12-disulphonic acid (VI).

From the results so far obtained it appears that 4-substituted fluoranthenes undergo further substitution mainly in the 11- or the 12-position according to whether the first substituent is *ortho-para-* or *meta*-directing. In harmony with this is the observation that 4-azafluoranthene gives a 12-nitro-derivative (Koelsch and Steinhauer, *J. Org. Chem.*, 1953, **18**, 1516). A possible explanation of these results may be found by considering



fluoranthene as a diphenyl derivative containing the diphenyl nuclei AC and BC. Now it is established in the diphenyl series that " constancy of type of substitution prevails," *i.e.*, orientation is dominated by the phenyl groups (Waters, *Chem. Rev.*, 1930, **7**, 421; Le Fèvre and Turner, *J.*, 1928, 245; Blakey and Scarborough, *J.*, 1928, 3000; Vorländer, *Ber.*, 1925, **58**, 1893). To be more specific, substitution in most cases occurs in the second ring in the 2'- and 4'-positions irrespective of the nature and position of the substituent already present in the first ring. The three nitrodiphenyls, for example, undergo substitution in the 2'- and 4'-positions, but not in the 3'(" meta ")-position. The same regularities are observed in the fluorene molecule. Applying this to fluoranthene it is reasonable to postulate that in (I) each of the

rings A and B directs substituents predominantly to the "*para*"-position in ring C, *i.e.*, to positions 11 and 12 respectively, and (2) an *ortho-para*-directing group in ring A increases the directive power of this ring with consequent substitution at $C_{(11)}$ (and possibly $C_{(13)}$), while *meta*-directing groups decrease the directive power of ring A so that ring B dominates further substitution, which therefore occurs at $C_{(12)}$ (and possibly $C_{(10)}$).

Experimental

12-*Bromo*-4-*nitrofluoranthene*.—Bromine (0·85 ml.) in nitrobenzene (1 ml.) was added dropwise at room temperature to 4-nitrofluoranthene (2 g.) in nitrobenzene (20 ml.) and the solution was stirred for 2 hr. The precipitate was dissolved in chlorobenzene, and the solution washed with aqueous sodium hydroxide and then with water. The volume of the dried (Na_2SO_4) solution was reduced and **12-*bromo*-4-*nitrofluoranthene*** (48%) separated and crystallised from chlorobenzene in orange-yellow needles, m. p. 216—218° (Found: N, 4·4; Br, 24·7. $C_{16}H_8O_2NBr$ requires N, 4·3; Br, 24·5%). The bromonitro-compound (1 g.) was boiled in ethanol (100 ml.) with iron powder (1 g.) and concentrated hydrochloric acid (10 ml.) for 4 hr., during which hydrochloric acid (5 ml.) and iron powder (0·5 g.) were added. The mixture was made alkaline with ammonia, poured into water, and extracted with chloroform. The extract with a little concentrated hydrochloric acid gave the amine hydrochloride, which with ammonia yielded **4-*amino*-12-*bromofluoranthene*** (73%), yellow needles [from light petroleum (b. p. 60—80°)], m. p. 161—163° (Found: C, 64·6; H, 3·3; N, 4·2. $C_{16}H_{10}NBr$ requires C, 64·9; H, 3·4; N, 4·7%).

The bromo-amine (0·6 g.) in acetic acid (5 ml.) was added slowly to a stirred solution of sodium nitrite (1 g.) in concentrated sulphuric acid (7 ml.) and after 1 hour's stirring the solution was poured into a boiling solution of freshly prepared cuprous bromide (1 g.) in 34% hydrobromic acid. The mixture was poured into water and extracted with benzene. The insoluble residue was boiled with benzene and the combined extracts were washed with water, dried (Na_2SO_4), and chromatographed on alumina. A buff-coloured band separated and on extraction with benzene yielded a solid which was chromatographed. A yellow band separated and yielded 4 : 12-dibromofluoranthene, yellow needles (from benzene–light petroleum), m. p. and mixed m. p. 165—168°.

Oxidation of **12-*Bromo*-4-*nitrofluoranthene*.**—Chromic acid (2 g.) in water (12 ml.) and acetic acid (8 ml.) was added to a cold stirred solution of the bromonitrofluoranthene (1 g.) in acetic acid (100 ml.), and the mixture stirred overnight. It was boiled (½ hr.) and half the solvent removed by distillation. The solution was poured into water and extracted with ether. The ether layer was extracted with aqueous sodium carbonate and the carbonate extract on acidification with hydrochloric acid gave **6-*bromo*-2-*nitrofluorenone*-1-*carboxylic acid*** (28%), yellow needles (from acetic acid), m. p. 260—266° (decomp.) (Found: N, 3·9; Br, 23·5. $C_{14}H_6O_5NBr$ requires N, 4·0; Br, 23·0%). The acid when heated in quinoline for 15 min. at 220° afforded 2-nitrofluorenone, m. p. and mixed m. p. 220°. The acid (0·09 g.) was boiled with a trace of copper bronze in pyridine for ½ hr. and poured into dilute hydrochloric acid. The suspension was extracted with benzene, and the benzene extract washed with sodium carbonate solution, then water, and dried (Na_2SO_4). Evaporation of the solvent gave 6-bromo-2-nitrofluorenone (15%), yellow needles (from acetic acid–methanol), m. p. 272—274° (Found: N, 4·7; Br, 24·9. Calc. for $C_{13}H_6O_3NBr$: N, 4·6; Br, 26·3%). The decarboxylation was evidently accompanied by a little debromination.

Synthesis of **6-*Bromo*-2-*nitrofluorenone*.**—It is reported that 2 : 7-dinitrofluorene is quantitatively reduced to the aminonitro-compound by bubbling hydrogen sulphide through a suspension of the compound in hot ammoniacal ethanol (Cislak and Hamilton, *J., Amer. Chem. Soc.*, 1931, **53**, 746). We found it essential to boil the ethanolic suspension of the pulverised dinitrofluorene before reduction and to use an extremely vigorous stream of hydrogen sulphide. This gave a 66% yield of the product. A quantitative yield was obtained only by reprocessing unchanged starting material.

2-Acetamido-7-nitrofluorenone (2 g.) was added slowly to bromine (20 ml.) in carbon tetrachloride (20 ml.), and the mixture was boiled for ½ hr., the volume being kept constant by addition of solvent. The cold mixture was washed with aqueous sodium hydroxide and then poured into chlorobenzene The carbon tetrachloride was boiled off and the residual chlorobenzene solution was washed with aqueous sodium hydroxide and then water. The dried solution (Na_2SO_4) was reduced in volume and **2-*acetamido*-3-*bromo*-7-*nitrofluorene*** (39%) separated and crystallised from xylene in yellow needles, m. p. 283—287° (Found: N, 7·9; Br, 22·6. $C_{15}H_{11}O_3N_2Br$ requires N, 8·1; Br, 23·0%). The acetamido-compound (1 g.) was

boiled for 4 hr. in ethanol (150 ml.) and concentrated hydrochloric acid (25 ml.), more acid (5 ml.) being added after 2 hr. The mixture was made alkaline with concentrated ammonia solution and poured into water. An orange precipitate of 2-amino-3-bromo-7-nitrofluorene (97%) separated. The amine (0·35 g.) in boiling acetic acid (5 ml.) was chilled rapidly and the suspension was slowly added to a stirred solution of sodium nitrite (1 g.) in concentrated sulphuric acid (7 ml.) at 20°. The mixture was stirred (1 hr.). Ethanol (10 ml.) and copper bronze (trace) were added and the mixture was gently heated until the temperature reached 80°. It was then poured into water and the aqueous suspension extracted with benzene. The extract was washed with water, dried (Na_2SO_4), and chromatographed. From the eluate *6-bromo-2-nitrofluorene* (19%), colourless needles (from acetic acid–ethanol), m. p. 207°, was obtained (Found: N, 5·2; Br, 28·1. $C_{13}H_8O_2NBr$ requires N, 4·8; Br, 27·6%). Sodium dichromate (0·18 g.) in water (0·5 ml.) and acetic acid (1·5 ml.) was slowly added to the bromonitrofluorene (0·06 g.) in boiling acetic acid (1·5 ml.). The mixture was boiled (1 hr.) and poured into ice-water. *6-Bromo-2-nitrofluorenone* (19%) separated as yellow needles (from acetic acid–ethanol), m. p. 272—274° (Found: N, 4·9; Br, 26·6%). When admixed with the bromonitrofluorenone prepared as above it gave no m. p. depression.

12-Bromo-4-cyanofluoranthene.—4-Amino-12-bromofluoranthene (1 g.) in acetic acid (12 ml.) was added slowly to a stirred solution of sodium nitrite (1 g.) in concentrated sulphuric acid (7 ml.) at 10°. The mixture was stirred (½ hr.) and poured into an aqueous solution of cuprous cyanide and potassium cyanide at 60°. The mixture was boiled (½ hr.) and poured into water and extracted with benzene. The benzene extract was washed with water, dried (Na_2SO_4) and chromatographed. The column gave a yellow zone which was extracted and on evaporation yielded 12-bromo-4-cyanofluoranthene, yellow needles (from ethanol), m. p. 222—224°, identical with the substance prepared from 4-cyanofluoranthene.

4-Cyanofluoranthene.—The following method for the preparation of this compound was found to be more satisfactory than that of von Braun and Manz (*Annalen*, **1931**, **488**, 111). 4-Bromofluoranthene (4·1 g.), freshly prepared cuprous cyanide (4·1 g.), pyridine (40 ml.), and benzyl cyanide (5 drops) were heated at 240° in a sealed-tube for 24 hr. The product was boiled with benzene and the cold mixture filtered. The precipitate was washed with dilute hydrochloric acid, followed by water, and was shown to be 4-carbamoylfluoranthene, colourless needles, m. p. 278—280° (Found: C, 84·3; H, 4·8; N, 5·9. Calc. for $C_{17}H_{11}ON$: C, 83·3; H, 4·5; N, 5·7%). It was previously described as a golden-brown substance, m. p. 271—273° (von Braun and Manz, *loc. cit.*). The original benzene filtrate was reduced to a small volume and chromatographed on alumina. Development with benzene gave a yellow band which on elution and evaporation gave 4-cyanofluoranthene (64%), m. p. 114—115°.

Bromination of 4-Cyanofluoranthene.—Bromine (0·23 ml.) in nitrobenzene (1 ml.) was added slowly to a stirred solution of 4-cyanofluoranthene (0·5 g.) in nitrobenzene (1 ml.). After 2 hr. the precipitate was filtered off, washed successively with benzene, sodium hydroxide solution, and water, and finally chromatographed on alumina with benzene as solvent and developer. Elution of a yellow zone yielded *12-bromo-4-cyanofluoranthene* (66%), yellow needles (from benzene–light petroleum), m. p. 222—225°, showing no depression when admixed with a sample prepared as above (Found: N, 4·6; Br, 26·6. $C_{17}H_8NBr$ requires N, 4·6; Br, 26·1%).

12-Bromofluoranthene-1-carboxylic Acid.—12-Bromo-4-cyanofluoranthene (0·65 g.), sodium hydroxide (0·5 g.), water (1·5 ml.), and ethylene glycol (10 ml.) were boiled (5 hr.), then poured into water, and the mixture was acidified and extracted with benzene. The benzene solution was shaken with sodium carbonate solution, and the carbonate extract on acidification gave a precipitate of crude acid. The acid (0·4 g.) was boiled in methanol (100 ml.) and concentrated sulphuric acid (3 ml.) for 18 hr. and poured into water. The precipitate was dissolved in benzene and the solution after being washed with sodium carbonate and water was chromatographed on alumina. Development with benzene gave one main yellow band which on elution yielded *methyl 12-bromofluoranthene-1-carboxylate*, yellow needles (from methanol), m. p. 171—173° (Found: Br, 22·6. $C_{18}H_{11}O_2Br$ requires Br, 23·6%). The ester (0·1 g.) was boiled for 12 hr. with sodium hydroxide (0·5 g.), methanol (10 ml.), and water (5 ml.) and on acidification yielded *12-bromofluoranthene-4-carboxylic acid*, yellow needles (from acetic acid or benzene), m. p. 318—321° (Found: Br, 24·1. $C_{17}H_9O_2Br$ requires Br, 24·6%).

Bromination of Fluoranthene-4-carboxylic Acid and its Methyl Ester.—The acid was obtained in 78% yield by hydrolysing 4-cyanofluoranthene (0·4 g.) with water (4 ml.), sulphuric acid (4 ml.), and acetic acid (8 ml.). Bromine (0·4 ml.) was added to the acid (0·7 g.) in acetic acid (20 ml.), and carbon tetrachloride (10 ml.) stirred at 25° for 5 hr. and kept overnight. It

was stirred for a further 8 hr. and again kept overnight. 12-Bromofluoranthene-4-carboxylic acid separated and crystallised from acetic acid in yellow needles, m. p. and mixed m. p. 320—323°.

Bromine (0·2 ml.) was added to methyl fluoranthene-4-carboxylate (0·7 g.) in carbon disulphide (10 ml.) and carbon tetrachloride (10 ml.) and after being stirred at 25° for 5 hr. the mixture was kept overnight. Removal of the solvent gave methyl 12-bromofluoranthene-4-carboxylate, which after being washed with sodium carbonate solution and then with water, crystallised from benzene–ethanol and then methanol (twice) as yellow needles, m. p. and mixed m. p. 168—170°.

4-Acetylfluoranthene.—Magnesium (0·33 g.), absolute ethanol (1·3 ml.), and carbon tetrachloride (0·1 ml.) were gently heated and the reaction which set in was allowed to continue for several minutes. Dry ether (9 ml.) was added and diethyl malonate (2 ml.) in ethanol (1·3 g.) and ether (2 ml.) was dropped into the solution. The solution was boiled for 1 hr. and into the cooled mixture a benzene solution of fluoranthene-4-carbonyl chloride (0·3 g.) was poured carefully. The mixture was boiled for 1 hr. and kept overnight. Removal of the solvents at reduced pressure gave a viscous oil, which was boiled for 4 hr. in glacial acetic acid (3 ml.), concentrated sulphuric acid (0·4 ml.), and water (2 ml.). The solution was kept overnight, neutralised by sodium hydroxide solution, and extracted with ether. The ether extract was washed with sodium carbonate solution, followed by water, and the dried ether extract (Na_2SO_4) on evaporation yielded 4-acetylfluoranthene (40%), pale yellow needles (from alcohol), m. p. 126—129°, not depressed when admixed with an authentic sample prepared from 4-cyanofluoranthene (Campbell and Easton, *J.*, 1949, 340).

Disulphonation of Fluoranthene.—Powdered fluoranthene (20 g.) was stirred into cold concentrated sulphuric acid (40 g.) and gently warmed until it had dissolved. The mixture was poured into water and neutralised with barium carbonate. After removal of the barium sulphate, the solution of the barium fluoranthenedisulphonate was carefully acidified by dilute sulphuric acid until no more barium sulphate was precipitated. The suspension was filtered through a bed of Filter-cel, and the filtrate neutralised with potassium hydroxide solution. The solution was evaporated to dryness under reduced pressure, leaving potassium fluoranthenedisulphonate as a pale yellow solid (Found: S, 15·2. Calc. for $C_{16}H_8O_6S_2K_2$: S, 14·6%). The yield was good though the product was probably contaminated with potassium sulphate. Partition chromatography showed that sulphonation under these conditions gives mainly the disulphonic acid, together with some monosulphonic acid and a trace of unchanged fluoranthene.

4 : 12-Dimethoxyfluoranthene.—The potassium fluoranthenedisulphonate (21·5 g.) and potassium hydroxide (50 g.) were fused in a stream of nitrogen, and the cooled melt was dissolved in water. Acidification followed by extraction with ether gave an extract, which was dried (Na_2SO_4) and evaporated to give crude 4 : 12-dihydroxyfluoranthene (44%), which can be purified by crystallisation from light petroleum. Methyl sulphate (0·9 g.) in a little water and *tert.*-butanol was added with stirring to dihydroxyfluoranthene (1 g.), sodium hydroxide (0·4 g.), and water (10 ml.). The mixture was stirred (1 hr.), boiled (2 hr.), poured into water, and extracted with ether. The ether layer was washed with sodium hydroxide solution and then water, and the solvent exchanged for benzene. The benzene solution was chromatographed and a yellow band separated which on elution yielded *4 : 12-dimethoxyfluoranthene* (49%), pale yellow plates, m. p. 158—159·5°, alone or when admixed with the dimethoxy-compound described below (Found: C, 82·8; H, 5·7. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·3%). Attempts to oxidise the substance to a disubstituted fluorenone-1-carboxylic acid were unsuccessful.

4 : 12-Diacetylfluoranthene (2 g.) in a 4% solution of perbenzoic acid in chloroform (100 ml.) was kept in the dark at room temperature for 10 days with occasional shaking. The solution was washed with aqueous sodium carbonate followed by water, and was dried (Na_2SO_4). Removal of the chloroform yielded the diacetate (1·04 g.), m. p. 125—130°, which was boiled with 10% sodium hydroxide (50 ml.) for 5 hr.; the mixture was filtered, acidified, and extracted with ether. The dried extract (Na_2SO_4) was treated with an ethereal solution (50 ml.) of diazomethane and kept overnight, and the ether removed. The residue in benzene was chromatographed and gave a yellow band which on elution afforded 4 : 12-dimethoxyfluoranthene, m. p. 156—157°, alone or admixed with the above dimethoxy-compound.

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Department of Chemistry, University of Edinburgh. [*Received, September 24th*, 1954.]

The Iodination of Glyoxaline.

By J. H. Ridd.

[Reprint Order No. 5870.]

A kinetic study has been made of the iodination of glyoxaline, by iodine in aqueous solution, at about pH 7. The rate equation consists of two terms, one suggesting the reaction of the glyoxaline anion with I^+ or H_2OI^+, and the other, involving dependence on the square of the glyoxaline concentration, indicating self-catalysis by glyoxaline.

The position of electrophilic substitution in glyoxaline appears to depend on the substituting agent; *e.g.*, iodination (Pauly and Arauner, *J. pr. Chem.*, 1928, **118**, 33) and diazo-coupling (Fargher and Pyman, *J.*, 1919, **115**, 217) lead to substitution at the 2-position, while bromination (Balaban and Pyman, *J.*, 1922, **121**, 947) leads to substitution at the 4(5)-position. It has been suggested that this is due to a difference in mechanism, the glyoxaline anion reacting initially at the 2-position, and the neutral molecule at the 4(5)-position (Brown, Duffin, Maynard, and Ridd, *J.*, 1953, 3937; Bassett and Brown, *J.*, 1954, 2701). The kinetics of the iodination have therefore been studied to determine whether they are consistent with the prior formation of the glyoxaline anion.

The iodination of the glyoxaline ring in histidine has already been studied kinetically by Li (*J. Amer. Chem. Soc.*, 1944, **66**, 225). However, this is an unsuitable guide to the behaviour of glyoxaline, for the amino-acid side chain greatly alters the reactivity of the glyoxaline ring, making it very resistant to iodination. Brunings (*ibid.*, 1947, **69**, 205) was thus unable to prepare *C*-iodohistidines under Li's kinetic conditions, obtaining only highly coloured compounds of uncertain composition. Li found that the reaction was buffer-catalysed, but did not separate the catalysed and the uncatalysed rate.

In the work now reported, catalysis by extraneous buffers has been avoided by using a large excess of glyoxaline, partially neutralised with perchloric acid, to buffer the solution. A solution of iodine in potassium iodide was added to this, and the reaction was followed by estimating the iodine concentration. The concentrations of glyoxaline and iodide ions were at least twenty times the iodine concentration, and so remained effectively constant during a kinetic run, in spite of the formation of iodide ions in the reaction. The reaction was then found to be of the first-order with respect to stoicheiometric iodine. Table 1

Table 1.*

10^2[GH]	10^2[$HClO_4$]	10^2[I^-]	10^3k_1	$10k_2$	10^2[GH]	10^2[$HClO_4$]	10^2[I^-	10^3k_1	$10k_2$
6·0	3·0	2·0	0·282	0·094	5·0	2·5	1·0	0·845	0·338
4·0	2·0	2·0	0·144	0·072	3·0	1·5	1·0	0·384	0·256
2·0	1·0	2·0	0·0492	0·0492	1·5	0·75	1·0	0·138	0·184
7·0	3·5	1·5	0·652	0·186	5·0	2·5	0·75	1·435	0·574
5·0	2·5	1·5	0·384	0·152	3·0	1·5	0·75	0·626	0·417
3·0	1·5	1·5	0·173	0·115	2·0	1·0	0·75	0·329	0·329
8·0	4·0	1·0	1·880	0·470	1·5	0·75	0·75	0·218	0·291

* Throughout, units of k_1 are $sec.^{-1}$; units of k_2 are $sec.^{-1}$ $mole^{-1}$ l.

gives details of a batch of kinetic runs, carried out under buffered conditions giving constant hydrogen-ion concentration, so that the order with respect to glyoxaline and iodide ions could be determined. In all runs, the temperature was 25°, and the ionic strength was brought to 0·05 by addition of sodium perchlorate. The concentrations of glyoxaline (here represented as GH), perchloric acid, and iodide ions are given in cols. 1—3; col. 4 gives the observed first-order rate coefficients (k_1), and the last column gives the second-order rate coefficients (k_2), obtained by dividing k_1 by the concentration of free glyoxaline in the solution.

Since k_2 is not constant at a single iodide-ion concentration, the reaction cannot be of first order with respect to the glyoxaline. In Fig. 1, k_2 is plotted against the free glyoxaline concentration in the solution. At each iodide-ion concentration, the values fall on a straight

line intersecting the axis, [GH] = 0, at a point above the origin. This shows that the reaction rate can be expressed as the sum of two terms, one of first order with respect to glyoxaline, and the other of second order : these will be referred to as the uncatalysed and the self-catalysed reaction respectively. The relative slopes and intercepts show that the rates of both reactions vary approximately as the inverse square of the iodide-ion concentration. When the logarithms of the slopes are plotted against log [I^-], the order is given as −2·1. The same value is obtained from a logarithmic plot of the intercepts, for iodide-ion concentrations of 0·01—0·02M, but the value for the 0·0075M-solutions lies below the line, and the order calculated from the two lowest iodide-ion concentrations is −1·4. For simplicity, subsequent experiments were restricted to iodide-ion concentrations equal to or above 0·01M, so that the inverse-square relation could be used.

FIG. 1.

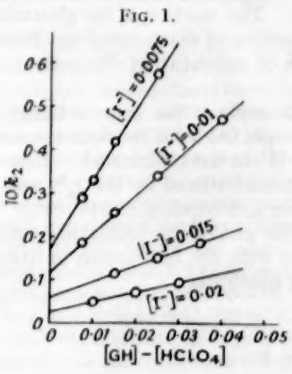

FIG. 2.

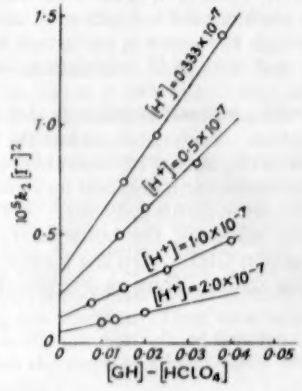

Table 2 gives the results of a number of runs carried out to determine the variation of k_2 with the hydrogen-ion concentration. The values quoted for [H^+] are calculated from the ratio [GH_2^+] : [GH], 10^{-7} being taken as the dissociation constant of the glyoxalinium cation (Albert, Goldacre, and Phillips, *J.*, 1948, 2240); however, this value is not critical, since the conclusions depend only on the relative hydrogen-ion concentrations. The second-order rate coefficients are calculated as in Table 1, and rendered independent of the iodide-

TABLE 2.

10^3[GH]	10^3[$HClO_4$]	10^3[I^-]	10^7[H^+]	10^3k_1	$10k_2$	10^5k_2[I^-]^2
5·0	1·25	2·0	0·333	1·323	0·353	1·412
3·0	0·75	2·0	0·333	0·536	0·238	0·952
2·0	0·5	2·0	0·333	0·278	0·185	0·740
4·8	1·6	1·5	0·5	1·174	0·367	0·826
3·0	1·0	1·5	0·5	0·553	0·276	0·621
2·1	0·7	1·5	0·5	0·307	0·219	0·493
6·0	4·0	1·0	2·0	0·274	0·137	0·137
4·0	2·66	1·0	2·0	0·141	0·106	0·106
3·0	2·0	1·0	2·0	0·095	0·095	0·095

ion concentration by multiplying by [I^-]^2. The values of k_2[I^-]^2 in the last column are plotted against the free glyoxaline concentration in Fig. 2, together with those values from Table 1 for [I^-] = 0·01. Since Table 1 refers to half-neutralised glyoxaline solutions, these values correspond to [H^+] = 10^{-7}. From the relative slopes and intercepts, it is found that both the self-catalysed and the uncatalysed reaction rate are inversely proportional to the hydrogen-ion concentration. When the logarithms of the slopes and intercepts are plotted against log [H^+], the order with respect to hydrogen ions is given as −1·0 for both. The full kinetic equation for the iodination is thus :

$$\text{Rate} = k[GH][I_3^-]/[H^+][I^-]^2 + k'[GH]^2[I_3^-]/[H^+][I^-]^2$$

Discussion.—Berliner's work on the iodination of aniline (*J. Amer. Chem. Soc.*, 1950, **72**, 4003) and phenol (*ibid.*, 1951, **73**, 4307) provides a guide to the interpretation of the kinetic equation. He showed that two reaction paths are present in buffered solutions, one involving iodination by I^+ or H_2OI^+, and the other being buffer-catalysed, possibly by the formation of alternative iodinating agents. Previously the neutral hypoiodous acid molecule had been considered as the iodinating species, but this should be a poor electrophilic reagent, and the results can be re-interpreted in favour of I^+ or H_2OI^+ (Ingold, " Structure and Mechanism in Organic Chemistry," Bell and Sons, London, 1953, p. 290). The species I^+ and H_2OI^+ are here considered as equivalent.

In the solutions used here, the stoicheiometric iodine is mainly present as I_3^-, so that the molecular iodine concentration varies as $[I^-]^{-1}$, and the concentrations of I^+ and H_2OI^+ as $[I^-]^{-2}$. The kinetics of the uncatalysed reaction, and, in particular, the order with respect to $[H^+]$ and $[I^-]$, agree with iodination by I^+ or H_2OI^+ on the glyoxaline anion, and rule out predominant iodination by molecular iodine. The reaction of the glyoxaline molecule through the anion is consistent with the mechanism of diazo-coupling (Brown *et al.*, *loc. cit.*) and with M.O. calculations on the position of substitution (Bassett and Brown, *loc. cit.*).

The self-catalysed reaction is clearly a special example of the general buffer catalysis of iodination. Such catalysis has the kinetic form expected from the formation of alternative iodinating agents by the substitution of I^+ for H^+ in the buffer acid. Thus in acetic acid, the kinetics fit iodination by IOAc, and in solutions buffered by HPO_4^{2-} and $H_2PO_4^-$, the buffer catalysis fits iodination by $IHPO_4^-$ (Painter and Soper, *J.*, 1947, 342). In these glyoxaline solutions, the buffer acid is GH_2^+, so the analogous iodinating agent is the *N*-iodo-cation GHI^+; and the kinetics are consistent with the interaction of this with the glyoxaline anion. Thus, as a result of the following equilibria:

$$I_3^- = I^- + I_2 \quad \ldots \quad (1)$$

$$I_2 + H_2O = H_2OI^+ + I^- \quad \ldots \quad (2)$$

$$GH = G^- + H^+ \quad \ldots \quad (3)$$

$$GH + H_2OI^+ = GHI^+ + H_2O \quad \ldots \quad (4)$$

the equation for the reaction rate can be rewritten in the form

$$\text{Rate} = k[G^-][H_2OI^+] + k'[G^-][GHI^+]$$

where k and k' now include the equilibrium constants for reactions (1)—(4).

If this interpretation is correct, the *N*-iodoglyoxalinium ion must be rapidly formed in a small equilibrium concentration. This presumably occurs by iodination at the unsubstituted " pyridine " nitrogen atom, to form a cation which can then attack the glyoxaline anion in the same way as any other carrier of I^+. However, this self-catalysed reaction is of special interest since its relative importance increases with the glyoxaline concentration, so that under preparative conditions it must largely determine the reaction rate and the position of substitution.

The foregoing discussion refers to the formation of the monoiodo-compound. However, analysis shows that even with a twenty-fold excess of glyoxaline, the main product is a di-iodoglyoxaline; hence the initial reaction must be rapidly followed by a second iodination. This implies that the observed rate coefficients are twice those of the initial reaction; however, the relative values, and hence the mechanistic discussion, are unaffected. The fact that the kinetics are of first order with respect to iodine (as I_3^-) shows that the rate-determining step is the formation of a monoiodo-compound. The rapid iodination of the monoiodo-compound can be understood if this also reacts through the anion, for while the ionised fraction is small, the greater concentration of the iodoglyoxaline anion can more than compensate for its lower reactivity.

Doak and Corwin (*J. Amer. Chem. Soc.*, 1949, **71**, 159) have shown that iodination of substituted pyrroles, in the presence of much greater iodide-ion concentrations, goes through molecular iodine. The relative importance of the I_2 and the H_2OI^+ mechanism

would be expected to depend jointly on the reactivity of the substrate and the iodide-ion concentration, so this is, in part, understandable. In our work, the deviation observed at the lowest iodide-ion concentration cannot be ascribed to a contribution from this mechanism, for the relative equilibrium concentrations of I_2 and H_2OI^+ do not then favour iodination by molecular iodine.

The kinetics of iodination of glyoxaline may be too complex to admit of a unique interpretation. Thus the uncatalysed reaction could be an internal rearrangement of a *N*-iodoglyoxaline to a *C*-iodo-product, and the catalysis by glyoxaline observed could be due to assisted proton loss in this transition state. However, there are a number of points in favour of the anion interpretation; it agrees with the diazo-coupling results, it is consistent with other studies on iodination, it explains the unreactivity of the *N*-methyl compound (Pauly and Gundermann, *Ber.*, 1908, **41**, 3999), and it provides a reason for the apparent change in the initial point of attack.

Experimental

The glyoxaline, recrystallised three times from benzene, had m. p. 89°. The iodine, potassium iodide, perchloric acid, and sodium thiosulphate were "AnalaR" reagents. The sodium perchlorate was dried at 120°, and stored in a vacuum desiccator.

Aqueous solutions of the reagents were prepared and diluted as required for the kinetic runs. The reaction was started by adding a solution of iodine in a twenty-fold excess of potassium iodide to a solution of glyoxaline partially neutralised with perchloric acid and containing, where necessary, sodium perchlorate and more potassium iodide. The solutions were kept in a thermostat at 25°, before and after mixing. The final volume was 100 ml., and the final iodine concentration was 0·0005M, except in the runs where $[I^-] = 0·0075$, where the iodine concentration was reduced to 0·000375. Samples (10 ml.) were withdrawn at suitable intervals and run into N-sulphuric acid (20 ml.), which stopped the reaction. They were immediately titrated with 0·002N-thiosulphate solution, with starch as an indicator. Good first-order kinetics were obtained, the rate constants being calculated from the slope of a logarithmic plot of the titre against time.

The analysis of the products was carried out on ten times the kinetic scale, and with the substitution of hydrochloric acid for perchloric acid, to prevent precipitation of potassium perchlorate on evaporation. The following concentrations were used: [GH] = 0·05, [HCl] = 0·025, $[I^-] = 0·05$, $[I_2] = 0·0025$. After two days the solution was evaporated to 50 ml., cooled, and filtered. The precipitate, after recrystallisation from water, had m. p. 182° (Found: C, 11·6; H, 0·8; N, 9·1; I, 80·0. Calc. for $C_3H_2N_2I_2$: C, 11·3; H, 0·6; N, 8·8; I, 79·4%).

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9 : 10-*Dihydrophenanthrenes. Part III.** *Optically Active* 9 : 10-*Dihydro*-3 : 4-5 : 6-*dibenzophenanthrene.*

By D. Muriel Hall and E. E. Turner.

(*With an Appendix on Theoretical Considerations of the Optical Stability of* 9 : 10-*Dihydrophenanthrene.* By K. E. Howlett.)

[Reprint Order No. 5915.]

The (+)- and the (−)-form of 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene with $[\alpha]_{4461}^{22}$ +1496° and −1500° in benzene have respectively been prepared from the (−)- and the (+)-form of 1 : 1′-dinaphthyl-2 : 2′-dicarboxylic acid *via* 2 : 2′-bishydroxymethyl-1 : 1′-dinaphthyl and 2 : 2′-bisbromomethyl-1 : 1′-dinaphthyl. The hydrocarbon is optically stable in benzene at 60° but racemises in boiling toluene with a half-life of 218 min. and in boiling ethylbenzene with a half-life of 13 min.

Optically active azepinium salts have also been prepared from the active 2 : 2′-bisbromomethyl-1 : 1′-dinaphthyl.

The optical stabilities of 2 : 2′-bridged dinaphthyls and diphenyls are discussed.

The method of preparation of 9 : 10-dihydrophenanthrene by the action of phenyl-lithium on 2 : 2′-bisbromomethyldiphenyl (Hall, Lesslie, and Turner, *J.*, 1950, 711) has been shown to be generally applicable to the synthesis of substituted 9 : 10-dihydrophenanthrenes (Hall and Turner, *J.*, 1951, 3072; Beaven, Hall, Lesslie, and Turner, *J.*, 1954, 131; Bergmann and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1951, **73**, 5153; Wittig and Zimmermann, *Chem. Ber.*, 1953, **86**, 629; Bergmann and Pelchowicz, *J. Amer. Chem. Soc.*, 1953, **75**, 2663). The molecule of 9 : 10-dihydrophenanthrene can be regarded as having a collinear diphenyl skeleton, with the two benzene rings twisted at an angle of about 20° in order to accommodate the two methylene groups without appreciable distortion (Beaven, Hall, Lesslie, and Turner, *J.*, 1952, 854). A substance having such a molecule should be capable of exhibiting enantiomorphism, although it is possible that the energy required to distort this simple molecule into a (temporary) planar configuration might be low enough to make the demonstration of optical activity experimentally difficult. We and our colleagues (Dr. M. S. Lesslie and Dr. M. M. Harris) have so far failed to resolve a 2-substituted 9 : 10-dihydrophenanthrene; and a calculation by Dr. K. E. Howlett (see Appendix) of the energy required for the racemisation of such a compound indicates that its optical activity is likely to be detectable only at very low temperatures.

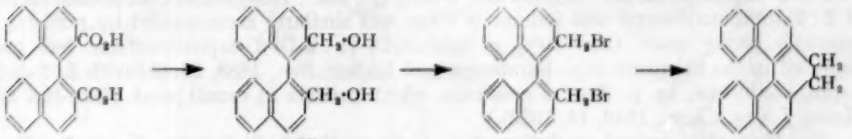
An alternative approach is to carry out the synthesis on an optically active 6 : 6′-disubstituted diphenic acid; in this case the steric requirements for optical activity in the diphenic acid ensure that the 9 : 10-dihydrophenanthrene will have 4 : 5-substituents leading to "intramolecular overcrowding." This phenomenon and the optical activity resulting from it are now well established in a number of compounds in which a normally planar molecule, *e.g.*, phenanthrene, becomes non-planar when 4 : 5-substituents are present (Newman and Hussey, *J. Amer. Chem. Soc.*, 1947, **69**, 978, 3023; Newman and Wheatley, *ibid.*, 1948, **70**, 1913; Bell and Waring, *Chem. and Ind.*, 1949, 321; *J.*, 1949, 2689; Theilacker and Baxmann, *Naturwiss.*, 1951, **38**, 156; *Annalen*, 1953, **581**, 117). These compounds all racemise readily, either at room temperature or, in the case of 1 : 8-diamino-4 : 5-dimethyl-9 : 10-diazaphenanthrene (Theilacker and Baxmann, *loc. cit.*), when kept in methanolic solution for 1 hr. at 60°.

A 9 : 10-dihydrophenanthrene with 4 : 5-substituents would be expected to be more stable optically than a similar phenanthrene, since racemisation would require the simultaneous passing of the 4- and the 5-substituent and of the two methylene groups.

* Part II, *J.*, 1951, 3072.

Nevertheless, racemisation might occur during any of the three stages in the synthesis from the optically active diphenic acid or in the final product before its isolation.

1 : 1′-Dinaphthyl-2 : 2′-dicarboxylic acid (I), which had been resolved by Kuhn and Albrecht (*Annalen*, 1928, **465**, 282), seemed suitable for our purpose and was accordingly made and resolved through the quinine salt. Decomposition of the less soluble salt gave the acid with $[\alpha]_{5461}^{22}$ −125·2° (in 0·1N-sodium hydroxide), and this was reduced with lithium aluminium hydride in ethereal solution to (−)-2 : 2′-bishydroxymethyl-1 : 1′-dinaphthyl (II), $[\alpha]_{5461}^{23}$ −83·0° in acetone. Treatment of this compound with hydrobromic acid in boiling glacial acetic acid gave (−)-2 : 2′-bisbromomethyl-1 : 1′-dinaphthyl (III), $[\alpha]_{5461}^{22}$ −199·1° in benzene. This rather drastic treatment was not, apparently, accompanied by appreciable racemisation, probably because the replacement reaction was very fast and the dibromide crystallised almost at once from the boiling solution. The (−)-dibromide was added to an ethereal solution of phenyl-lithium and, after treatment with water and



(I) (II) (III) (IV)

evaporation of the ether at room temperature, impure (+)-9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene (IV) was isolated. The recrystallised material had the surprisingly high specific rotation of $[\alpha]_{5461}^{22}$ +1496° in benzene. A preliminary account of this part of the work has been given in *Chem. and Ind.*, 1953, 1177. In benzene solution the hydrocarbon was optically stable at 60° and only very slowly racemised (sealed tube) at 100°. It had a half-life of 218 min. in boiling toluene and of 13 min. in boiling ethylbenzene. It melted at 183° with complete and rapid racemisation.

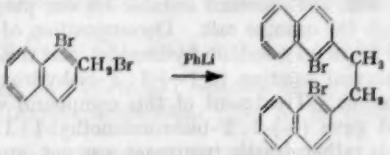
Similar treatment of the acid ($[\alpha]_{5461}^{20}$ +124·2° in 0·1N-sodium hydroxide) obtained from the more soluble quinine salt gave the (+)-diol, $[\alpha]_{5461}^{23}$ +83·1° in acetone, and thence the (+)-dibromide, $[\alpha]_{5461}^{23}$ +198·8° in benzene, and the (−)-hydrocarbon, $[\alpha]_{5461}^{22}$ −1500° in benzene.

In a similar series of reactions starting with optically active 6 : 6′-dimethyl-2 : 2′-diphenic acid, Wittig and Zimmermann (*loc. cit.*) obtained (after distillation) optically inactive 9 : 10-dihydro-4 : 5-dimethylphenanthrene from the active dibromide; but they nevertheless demonstrated indirectly that the molecule of this hydrocarbon is dissymmetric since they isolated two racemic and three of the four possible optically active forms of 9 : 10-dihydro-4 : 5-dimethylphenanthryltrimethylammonium iodide.

When we had completed all but the last stage of the trial synthesis of the racemic compound, Bergmann and Szmuszkovicz (*loc. cit.*) published a similar synthesis of the racemic compound, differing from ours only in certain experimental details. Attention is drawn to these in the Experimental section. In particular we found that the yield of 1-bromo-2-naphthaldehyde from 1-bromo-2-bromomethylnaphthalene (Hewett, *J.*, 1940, 293) was much improved by the use of the technique for the Sommelet reaction described by Angyal, Morris, Tetaz, and Wilson (*J.*, 1950, 2141).

We also investigated a number of short cuts and one alternative synthesis of (±)-dihydrodibenzophenanthrene, but all were unsuccessful. Thus, neither 1-bromo-2-methylnaphthalene nor 1-bromo-2-bromomethylnaphthalene could be oxidised to 1-bromo-2-naphthoic acid. A Grignard reagent was made from 1-bromo-2-methylnaphthalene and treated with anhydrous cupric chloride but no crystalline product was isolated. 1-Bromo-2-naphthaldehyde was heated with copper powder but no solid product was obtained. The aldehyde failed to undergo a Cannizzaro reaction and was extremely resistant to the usual oxidising agents (chromic anhydride in glacial acetic acid; nitric acid; hydrogen peroxide; aqueous potassium permanganate). Oxidation was achieved by the use of an excess of aqueous potassium permanganate in acetone solution at $\gtrsim$70°, and under these conditions was rapid and practically quantitative. As an alternative route we prepared

1 : 2-di-(1-bromo-2-naphthyl)ethane by the action of phenyl-lithium on 1-bromo-2-bromomethylnaphthalene and tried to induce ring closure to dihydrodibenzophenanthrene by the action of various metals :



The dibromo-compound was unaffected by magnesium turnings or by copper bronze at 290°. The use of copper at higher temperatures gave a gum. Sodium in boiling toluene or, better, boiling di-*n*-butyl ether, removed the bromine without ring-closure, producing 1 : 2-di-2′-naphthylethane. Kenner and Wilson (*J.*, 1927, 1108) found that the interaction of 2 : 2′-dibromodibenzyl and sodium in ether was similarly accompanied by removal of bromine, giving more than 50% of dibenzyl. [1 : 2-Di-2′-naphthylethane has been confused in the literature (*e.g.*, Bamberger and Lodter, *Ber.*, 1888, **21**, 51) with 1 : 2-di-2′-naphthylethylene, m. p. 254°, a confusion which persists in recent work (Buu-Hoï and Hoán, *J. Org. Chem.*, 1949, **14**, 1023).]

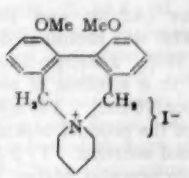
The large-scale optical resolution of 1 : 1′-dinaphthyl-2 : 2′-dicarboxylic acid differed in a number of features from the small-scale resolution described by Kuhn and Albrecht (*loc. cit.*). The latter authors crystallised the quinine salt (from 0·8 g. of acid) from ethanol–ether and obtained crops with $[\alpha]_D^{22}$ +230·4°, $[\alpha]_D^{24}$ +301·6° and, by total evaporation, $[\alpha]_D^{22\cdot6}$ +15·4° in chloroform. Decomposition of the second and third crops gave the acid with $[\alpha]_D^{22}$ −101·6° and $[\alpha]_D^{22}$ +46° in 0·1N-sodium hydroxide. We found that once the two diastereoisomerides had been obtained crystalline, they could be crystallised from ethanol without the addition of ether, but the resolution was complicated by the following factors : (*a*) the specific rotation of the salts in chloroform was extremely sensitive to the presence of traces of ethanol, *e.g.*, a crop with $[\alpha]_{5461}$ −29·1° in " B.P." chloroform had $[\alpha]_{5461}$ +10·0° in chloroform which had been freed from ethanol; (*b*) both salts were solvated with ethanol and thus the specific rotation in chloroform was affected by the actual weight of salt used for determining the specific rotation (after this had been discovered, all specific rotations were determined in acetone solution); and (*c*) the specific rotation of the salt of the (−)-acid had a fairly large temperature coefficient, the salt becoming more lævorotatory with rise in temperature.

The less soluble salt had $[\alpha]_{5461}^{22}$ about −36° in washed chloroform and −103·5° in acetone. It seems likely that Kuhn and Albrecht's salt was not solvated and that the strong dextrorotation which these authors observed is that of the unsolvated salt in chloroform entirely free from ethanol. That this corresponds to our *lævo*-salt is shown by the fact that both gave the *lævo*-acid. Our acid had $[\alpha]_{5461}^{22}$ −125·2°, $[\alpha]_{5791}^{22}$ −108·6°, and theirs had $[\alpha]_D^{22}$ −101·6°, all in 0·1N-sodium hydroxide. Our more soluble salt had $[\alpha]_{5461}^{22}$ about +75° in washed chloroform and +11·6° in acetone. It would presumably be much more strongly dextrorotatory in chloroform entirely free from ethanol (*i.e.*, if unsolvated salt could be used). Kuhn and Albrecht describe the more soluble salt as having $[\alpha]_D$ +15° in chloroform, but it is apparent from the quantities given that they in fact used an excess of quinine, which would be present in the total material obtained on evaporation and would account for the very low dextrorotation. Decomposition of our more soluble salt gave acid with $[\alpha]_{5461}^{20}$ +124·2°, $[\alpha]_{5791}^{20}$ +107·2° in 0·1N-sodium hydroxide. Kuhn and Albrecht were, of course, concerned only in showing that the acid could exist in enantiomorphic forms.

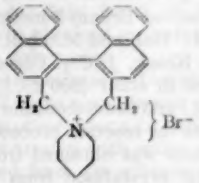
1 : 1′-Dinaphthyl-2 : 2′-dicarboxylic acid is optically highly stable (Kuhn and Albrecht, *loc. cit.*; Hall, Ridgwell, and Turner, *J.*, 1954, 2498) and we have so far failed to racemise it. For example, the rotation was unchanged after the acid had been heated in *N*-methylformamide at *ca.* 175° for 8 hr. and, although the solution developed an intense fluorescence, the acid appeared to be mainly unchanged chemically. It remained optically active after being in solution for 2 hr. in boiling tetralin; the development of colour in the solution and

the low solubility of the acid in cold tetralin made it impossible to discover if slight racemisation had occurred. In boiling ethylene glycol solution, however, the acid underwent chemical change with some loss of optical activity.

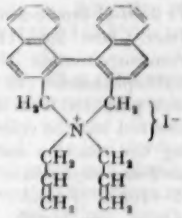
Discussion of Specific Rotations and Optical Stabilities.—2 : 7-Dihydro-4' : 1''-dimethoxy-3 : 4-5 : 6-dibenzazepinium-1-*spiro*-1'''-piperidinium iodide (V) has a very small specific rotation ($[\alpha]_{5461}^{20}$ +4·0° and −3·8°) (Beaven, Hall, Lesslie, and Turner, *J.*, 1952, 854) and it seemed possible that this might be a common property of diphenyls bridged in the 2 : 2'-positions to form 6- and 7-membered rings. This expectation is not borne out by the large specific rotation of 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene. We therefore prepared (+)-2 : 7-dihydrodinaphtho(2' : 1'-3 : 4)(1'' : 2''-5 : 6)azepinium-1-*spiro*-1'''-piperidinium bromide (VI) and (+)-1 : 1-diallyl-2 : 7-dihydrodinaphtho(2' : 1'-3 : 4)-



(V)



(VI)



(VII)

(1'' : 2''-5 : 6)azepinium iodide (VII) in which the 2 : 2'-positions are linked to form 7-membered heterocyclic rings. These compounds have $[\alpha]_{5461}^{20}$ +306·5° and +205·3° respectively in ethanol.

It is likely that the high values of [α] observed with the spirans (VI) and the closely related compound (VII) compared with the value for (V) are associated with larger contributions to the optical rotatory power from the absorption bands nearest the visible region.

In each case the *lævo*-dibromide (III) gave a *dextro*-compound on cyclisation (IV, VI, and VII).

Compound (VI) underwent racemisation in hot ethylene glycol solution. It had a half-life of the order of 26 hr. at 172°. In *N*-methylformamide solution at the same temperature racemisation was much faster, being complete in about 6 hr., but was accompanied by chemical change and none of the original bromide could be recovered.

The optical stability of 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene is of particular interest. On the one hand it is much more stable optically than 3 : 4-5 : 6-dibenzophenanthrene-9 : 10-dicarboxylic acid, the morphine salt of which exhibits mutarotation in chloroform solution but gives an optically inactive acid (Bell and Waring, *loc. cit.*). On the other hand, both the hydrocarbon and the corresponding 7-membered-ring compound (VI) are less stable optically than the non-bridged 1 : 1'-dinaphthyl-2 : 2'-dicarboxylic acid; but it is probably not valid to compare the effect of linked methylene groups with that of free carboxyl groups and a more interesting comparison would be with the so far unknown 2 : 2'-dimethyl-1 : 1'-dinaphthyl. Enlargement of the bridging ring from 6 atoms in (IV) to 7 atoms in (VI) leads to a considerable increase in optical stability; the groups causing steric interference are the same in both compounds but much greater distortion is required to enable the 7-membered ring to pass through the planar configuration. This is reflected in the optical stability of the azepinium compound (V) in which the substituents in the 4 : 5-positions are methoxyl groups instead of benzene rings. This compound, although less optically stable than its analogue (VI), is nevertheless more stable than the hydrocarbon (IV), despite the fact that the purely blocking effects of its *ortho*-substituents are much smaller. [The half-life of (V) is of the order of 3—4 hr. at 160°; cf. Beaven, Hall, Lesslie, and Turner, *loc. cit.*).] This confirms us in our view that the optical activity and high optical stability of the spiran (V) are primarily due to the configurational stability of the 7-membered ring.

It thus appears that the passage through the planar configuration of a molecule of the

ortho-substituted diphenyl type is facilitated by the joining of two of the blocking groups into a ring; and, further, that the planar configuration is more easily achieved when the angle between the ring planes is already small, as in compound (IV), than when it is of the order of 50°, as in compounds (V) and (VI).

The case of 4 : 5-disubstituted phenanthrenes is rather different, since the phenanthrene system is distorted from the preferred coplanar configuration (*e.g.*, 3 : 4-5 : 6-dibenzophenanthrene in the crystal; McIntosh, Robertson, and Vand, *Nature*, 1952, **169**, 322; *J.*, 1954, 1661) and therefore has a greater inducement to become flat than has a substituted dihydrophenanthrene in which the *preferred* configuration is non-planar.

Experimental

In all polarimetric readings $l = 2$.

1 : 2-*Di*-(1-*bromo*-2-*naphthyl*)*ethane*.—1-Bromo-2-methylnaphthalene (Adams and Binder, *J. Amer. Chem. Soc.*, 1941, **63**, 2773; Hall and Mitchell, *J.*, 1951, 1375) was brominated with *N*-bromosuccinimide (Newman and Kosak, *J. Org. Chem.*, 1949, **14**, 375). 1-Bromo-2-bromomethylnaphthalene (48 g.), dissolved in ether (800 c.c.), was added to a solution of phenyllithium, prepared from lithium (1·5 g.) and bromobenzene (16 g.) in ether (75 c.c.). The solution became red but the colour was lost as the reaction proceeded. Most of the product crystallised during the reaction and a little more was obtained from the ethereal solution. 1 : 2-*Di*-(1-*bromo*-2-*naphthyl*)*ethane* (21 g., 60%) crystallised from benzene in rectangular plates, m. p. 192·5—193·5° (Found: Br, 36·2. $C_{22}H_{16}Br_2$ requires Br, 36·3%).

Action of Metals on 1 : 2-*Di*(1-*bromo*-2-*naphthyl*)*ethane*.—(a) *Copper*. The dibromo-compound was heated with copper bronze at 270—290° for 1 hr. and the resulting mixture extracted with acetone. Only unchanged dibromo-compound could be isolated. When reaction was carried out at 310—320° very little of the dibromo-compound was recovered and the product was a gum.

(b) *Magnesium*. The dibromo-compound did not form a Grignard reagent with magnesium in boiling di-*n*-butyl ether (14 hr.).

(c) *Sodium*. The dibromo-compound (1·65 g.) was dissolved in warm di-*n*-butyl ether (30 c.c.), and sodium (1 g.) added. Reaction started on warming; the ether was slowly heated to the b. p. and gentle boiling was continued for 5 hr. The mixture was filtered hot; the filtrate deposited a bromine-free solid (0·5 g.) which, after crystallisation from light petroleum (b. p. 60—80°), had m. p. 185—186° (Found: C, 93·2; H, 6·4. Calc. for $C_{22}H_{18}$: C, 93·6; H, 6·4%), and gave a picrate, m. p. 198—199°. 1 : 2-Di-2′-naphthylethane has m. p. 182—184° and its picrate m. p. 198° (Friedmann, *Ber.*, 1916, **49**, 1352).

1-*Bromo*-2-*naphthaldehyde*.—1-Bromo-2-bromomethylnaphthalene (90 g.) was dissolved in chloroform (400 c.c.), and powdered hexamine (46·5 g.) added in several lots to the boiling solution. The hexaminium salt (128 g.) separated in a few minutes and was filtered off and then boiled in 50% acetic acid (650 c.c.) for 1 hr. Concentrated hydrochloric acid (105 c.c.) was added and the solution boiled for 5 min. The aldehyde (41 g., 58%), m. p. 119—120°, crystallised on cooling. The *semicarbazone*, m. p. >270°, crystallised from glacial acetic acid (Found: N, 12·1; Br, 22·7. $C_{13}H_{10}ON_3Br,CH_3{\cdot}CO_3H$ requires N, 11·9; Br, 22·7%).

1-*Bromo*-2-*naphthoic Acid*.—A solution of 1-bromo-2-naphthaldehyde (11 g.) in acetone (275 c.c.) was heated in a bath kept at 60—68°; a hot aqueous solution of potassium permanganate (14 g. in 330 c.c.) was added during ½ hr. and heating was continued for a further ½ hr. Sulphur dioxide was passed in at once and the clear solution poured into water (1·5 l.). The crude acid from 30 oxidations was taken through the ammonium salt (the sodium salt was very sparingly soluble in water) and reprecipitated, giving 307 g. (87%), m. p. 189—191°. Bergmann and Szmuszkovicz (*loc. cit.*), using different experimental conditions, obtained a rather lower yield of acid, m. p. 186°.

Dimethyl 1 : 1′-*Dinaphthyl*-2 : 2′-*dicarboxylate*.—1-Bromo-2-naphthoic acid was esterified by boiling methanol and sulphuric acid (yield 89%), and the ester heated with copper bronze at 270—280° for *ca.* 20 min. While still hot the mixture was extracted with toluene; the filtrate deposited crystals on cooling. A further crop was obtained by removal of some of the solvent. After one recrystallisation from ethanol the ester had m. p. 158° (yield 78%). (Martin, *J.*, 1941, 679, obtained a lower yield of the ester by heating for 5 hr. at 190°.)

1 : 1′-*Dinaphthyl*-2 : 2′-*dicarboxylic acid*, obtained by hydrolysis of the ester, crystallised from ethanol in a solvated form; prolonged heating on a steam-bath gave the anhydrous acid, m. p. 272—274°.

2 : 2′-*Bishydroxymethyl*-1 : 1′-*dinaphthyl*.—The above ester (20 g., 1 mol.) was ground and washed with ether (500 c.c.) into lithium aluminium hydride (5·4 g., 2·6 mols.) in ether (350 c.c.). After ½ hour's boiling the mixture was treated with water and sulphuric acid (2N), and the ether was distilled off. The diol was filtered off from the residual aqueous solution and crystallised from ethanol, giving 16 g. (94%), m. p. 191—192·5°.

2 : 2′-*Bisbromomethyl*-1 : 1′-*dinaphthyl*.—The above diol (10 g.) was dissolved in boiling glacial acetic acid (250 c.c.), and boiling hydrobromic acid (*d* 1·49; 75 c.c.) was added. The initial cloudiness disappeared but reappeared after ½ min. as the dibromide began to separate as an oil. The mixture was boiled for 15 min.; more hydrobromic acid (50 c.c.) was added and the boiling continued for another ½ hr. During this process the oil solidified and, after cooling, the solid was separated and crystallised from ethyl methyl ketone (yield 12 g., 86%). The dibromide formed large crystals, melting over a range of 10°, presumably owing to poor thermal conduction. When ground it melted at 151—153° to an opaque liquid which cleared at 155° (Found: C, 59·9; H, 4·0; Br, 36·1. Calc. for $C_{22}H_{16}Br_2$: C, 60·0; H, 3·7; Br, 36·3%). Bergmann and Szmuszkovicz (*loc. cit.*) obtained a product with m. p. 148—149·5° by treating the diol with phosphorus tribromide in benzene.

9 : 10-*Dihydro*-3 : 4-5 : 6-*dibenzophenanthrene*.—The above dibromide (25 g., 0·8 mol.) was added as a suspension in ether (500 c.c.) to a solution of phenyl-lithium, prepared from lithium (1·07 g.) and bromobenzene (11 g.) in ether (50 c.c.). After being heated for 1 hr., the solution was decanted through glass wool and treated with water and dilute acid. 9 : 10-Dihydro-3 : 4-5 : 6-dibenzophenanthrene crystallised from the ethereal solution, and more was obtained by evaporation of the solvent. It recrystallised from benzene or ethyl methyl ketone as needles, m. p. 215—216° (yield of pure material 9·5 g., 59%) (Found: *M*, 260. Calc. for $C_{22}H_{16}$: *M*, 280). Bergmann and Szmuszkovicz (*loc. cit.*) give m. p. 212—213°.

Resolution of 1 : 1′-*Dinaphthyl*-2 : 2′-*dicarboxylic Acid*.—The de-solvated acid (46·8 g., 1 mol.) and anhydrous quinine (44·3 g., 1 mol.) were dissolved together in ethanol (455 c.c.), and ether (455 c.c.) was added. The solution was kept at 4° and eventually deposited a salt (57 g.) which was subsequently recrystallised 3 times from ethanol to constant specific rotation (4 g.). The mother-liquor from the first crop was evaporated to dryness and the residue crystallised from ethanol. The more soluble salt was crystallised from highly concentrated ethanolic solutions. Intermediate crops were repeatedly recrystallised. Altogether 27·5 g. of the less soluble salt and 13·4 g. of the more soluble salt were obtained, apparently optically pure or nearly so. The less soluble *quinine salt* had m. p. 178° (decomp.), $[\alpha]_{5461}^{23}$ −103·5°, $[\alpha]_{5791}^{23}$ −89·8° (*c*, 1·101 in acetone) (Found: C, 74·15; H, 6·4. $C_{42}H_{38}O_6N_2,C_2H_5{\cdot}OH$ requires C, 74·1; H, 6·2%). The more soluble *quinine salt* had m. p. 184—190° (decomp.) with previous softening, $[\alpha]_{5461}^{23}$ +11·6°, $[\alpha]_{5791}^{23}$ +8·6° (*c*, 0·989 in acetone) (Found: C, 73·2; H, 6·4. $C_{42}H_{38}O_6N_2,1{\cdot}5C_2H_5{\cdot}OH$ requires C, 73·45; H, 6·4%). Several crops of the more soluble salt were obtained with $[\alpha]_{5461}$ about +21°, but decomposition gave acid which was not optically pure. Some of the (+)-acid with the highest [α] was therefore converted into the quinine salt and this had $[\alpha]_{5461}^{23}$ +11·6°. The higher dextrorotations obtained for the optically impure salt remain anomalous.

(−)-1 : 1′-*Dinaphthyl*-2 : 2′-*dicarboxylic Acid*.—A solution of the less soluble quinine salt (3·5 g.) in chloroform (35 c.c.) was extracted 3 times with N-potassium hydroxide. The combined extracts were washed with chloroform and poured into dilute hydrochloric acid. The precipitated (−)-1 : 1′-*dinaphthyl*-2 : 2′-*dicarboxylic acid* was crystallised from aqueous acetone (yield, 1·6 g.) and had $[\alpha]_{5461}^{22}$ −125·2°, $[\alpha]_{5791}^{22}$ −108·6° (*c*, 1·023 in approx. 0·1N-NaOH). It was hydrated, the analysis corresponding to about $0{\cdot}5H_2O$, and had m. p. *ca.* 120° (decomp.) (Found: C, 74·9; H, 4·5. $C_{22}H_{14}O_4,0{\cdot}5H_2O$ requires C, 75·2; H, 4·3%). It lost water when heated for some hours at 100° *in vacuo* but the anhydrous acid was very hygroscopic; to ensure reproducible results samples (*e.g.*, those obtained by precipitation) were always crystallised from aqueous acetone and air-dried at room temperature before their specific rotations were measured. The active *acid* also crystallised in needles, solvated with carbon tetrachloride, but apart from this could not be crystallised from anhydrous solvents (Found: C, 60·5; H, 3·6. $C_{22}H_{14}O_4,0{\cdot}7CCl_4$ requires C, 60·6; H, 3·1%).

(+)-1 : 1′-*Dinaphthyl*-2 : 2′-*dicarboxylic Acid*.—Similar decomposition of the more soluble quinine salt gave (+)-*acid*, m. p. *ca.* 120° (decomp.), $[\alpha]_{5461}^{20}$ +124·2°, $[\alpha]_{5791}^{20}$ +107·2° (*c*, 1·115 in approx. 0·1N-NaOH) (Found: C, 74·9; H, 4·6. $C_{22}H_{14}O_4,0{\cdot}5H_2O$ requires C, 75·2; H, 4·3%). Decomposition of the salt with $[\alpha]_{5461}$ *ca.* +21° gave acid with $[\alpha]_{5461}$ +84°, from which it proved possible to extract more highly active acid ($[\alpha]_{5461}$ +117°) with ether, the racemic acid being very sparingly soluble.

Attempted Racemisation of (+)-1 : 1′-*Dinaphthyl*-2 : 2′-*dicarboxylic Acid*.—(*a*) A solution of

the acid in 0·1N-sodium hydroxide, having α_{5461}^{20} +1·89°, was boiled under reflux for 10 hr. and then heated at 140° (sealed tube) for 5 hr. It then had α_{5461}^{20} +1·88°.

(*b*) A solution of the acid in *N*-methylformamide (α_{5461}^{21} +4·24°) was maintained at *ca.* 175° in an electrically heated bath. The solution became yellow and fluorescent. After 1·5 hr. it had α_{5461}^{20} +4·32° and after 8 hr. α_{5461}^{24} +4·3° ± 0·1°. (The small initial increase in α resulted from slight loss of solvent into the condenser.) Solid was recovered from the solution, and almost all of it dissolved readily in sodium hydrogen carbonate solution and was reprecipitated by acid.

(*c*) The acid ($[\alpha]_{5461}$ +110° in 0·1N-NaOH) dissolved in warm tetralin but crystallised out at room temperature. A 1% solution was heated at the b. p. for 2 hr., then cooled, and the acid was extracted with 0·1N-sodium hydroxide. The alkaline solution, which was green, was made up to 20 c.c. and had α_{5461} *ca.* 2·0°, corresponding to $[\alpha]_{5461}$ *ca.* 100°, indicating that little, if any, racemisation had occurred.

(*d*) The acid was boiled under reflux in ethylene glycol solution for 6 hr. Attempted recovery of the acid gave a gum, most of which was insoluble in alkali. The soluble part formed a colloidal solution, which cleared on the addition of acetone and was optically inactive.

(−)-2 : 2′-*Bishydroxymethyl*-1 : 1′-*dinaphthyl*.—The (−)-acid (12·0 g.), dissolved in ether (400 c.c.), was added to lithium aluminium hydride (5·1 g., 4 mols.) in ether (300 c.c.). The mixture was boiled for 1½ hr. Ethyl acetate was added, followed by water and 2N-sulphuric acid. The ethereal layer was separated, the solvent removed, and the residue crystallised twice from benzene. (−)-2 : 2′-*Bishydroxymethyl*-1 : 1′-*dinaphthyl* (9·1 g., 85%) was obtained as thick hexagonal plates, m. p. 168—169°, and also as solvated rods which readily lost solvent at 100° and then also had m. p. 168—169° (Found : C, 84·5; H, 5·7. $C_{22}H_{18}O_2$ requires C, 84·05; H, 5·8%). The diol had $[\alpha]_{5461}^{23}$ −83·0°, $[\alpha]_{5791}^{23}$ −72·3° (*c*, 0·9815 in acetone). The melted diol solidified on cooling and remelted at 168°, showing that racemisation had not occurred on melting.

(+)-2 : 2′-*Bishydroxymethyl*-1 : 1′-*dinaphthyl*.—Similar reduction of the (+)-acid (5·8 g.) gave the (+)-*diol* (4·5 g.), m. p. 167—168°, $[\alpha]_{5461}^{21}$ +83·1°, $[\alpha]_{5791}^{21}$ +72·2° (*c*, 1·1495 in acetone) (Found : C, 84·2; H, 6·0%).

(−)-2 : 2′-*Bisbromomethyl*-1 : 1′-*dinaphthyl*.—The (−)-diol (7·85 g.) was dissolved in boiling glacial acetic acid (195 c.c.), and boiling hydrobromic acid (*d* 1·49; 60 c.c.) was added. The solution cleared on shaking, then became cloudy and, after a few minutes' boiling, crystals separated. More hydrobromic acid (40 c.c.) was added and heating was continued for a total time of 7 min. after first adding hydrobromic acid. After cooling, the solid was filtered off, washed with water and dried *in vacuo* over sodium hydroxide. The crude *dibromide* (10·8 g., 98%) had m. p. 184—186°, $[\alpha]_{5461}^{21}$ −196·9° in C_6H_6, and was used without further purification. Some was recrystallised from ethyl methyl ketone and had m. p. 185·5—186·5°, $[\alpha]_{5461}^{20}$ −199·1°, $[\alpha]_{5791}^{20}$ −169·4° (*c*, 1·095 in C_6H_6) (Found : C, 59·7; H, 3·95; Br, 36·1. $C_{22}H_{16}Br_2$ requires C, 60·0; H, 3·7; Br, 36·3%).

(+)-2 : 2′-*Bisbromomethyl*-1 : 1′-*dinaphthyl*.—Similar treatment of the (+)-diol (3·7 g.) gave the (+)-*dibromide* which, after crystallisation from ethyl methyl ketone, had m. p. 185·5—186·5°, $[\alpha]_{5461}^{22}$ +198·8°, $[\alpha]_{5791}^{23}$ +169·9° (*c*, 1·089 in C_6H_6) (Found : C, 60·0; H, 4·1; Br, 36·0%).

(+)-9 : 10-*Dihydro*-3 : 4-5 : 6-*dibenzophenanthrene*.—The (−)-dibromide (4·0 g., 0·8 mol.) was added as a suspension in ether (100 c.c.) to a solution of phenyl-lithium, prepared from lithium (0·17 g.) and bromobenzene (1·8 g.) in ether (8 c.c.). After being heated for 35 min. the ethereal solution was decanted through glass wool and treated with water and dilute acid. The ethereal layer was separated and the ether removed at *ca.* 5°. The residual solid was crystallised twice from ethyl methyl ketone and yielded (+)-9 : 10-*dihydro*-3 : 4-5 : 6-*dibenzophenanthrene*, $[\alpha]_{5461}^{23}$ +1496°, $[\alpha]_{5791}^{23}$ +1302° (*c*, 0·5285 in C_6H_6) (Found : C, 94·0; H, 5·9. $C_{22}H_{16}$ requires C, 94·25; H, 5·75%), as thick hexagonal plates. These melted at 183° and at once resolidified as needles which then melted at 215—216° (the m. p. of the racemate).

(−)-9 : 10-*Dihydro*-3 : 4-5 : 6-*dibenzophenanthrene* was prepared similarly from the (+)-dibromide (3·85 g.). It had m. p. 183° (with second melting at 215—216°), $[\alpha]_{5461}^{23}$ −1500°, $[\alpha]_{5791}^{23}$ −1307° (*c*, 0·5250 in C_6H_6) (Found : C, 94·1; H, 6·0%).

Racemisation of (+)- *and* (−)-9 : 10-*Dihydro*-3 : 4-5 : 6-*dibenzophenanthrene*.—(*a*) No racemisation occurred with a solution of the (+)-compound in benzene at 60° for 24 hr.

(*b*) When a solution of the (+)-compound in benzene was heated in a sealed tube at 100° for 35 min. a small fall in rotation (*ca.* 3%) occurred.

(*c*) The rate of racemisation in boiling toluene solution was measured by using a solution (30 c.c.) containing 0·0803 g. of the (+)-compound. The temperature of the solution was raised rapidly to the b. p. and, after a suitable interval, the solution was rapidly cooled in ice-water. Polarimetric readings were taken at room temperature (22°) and the solution

returned to the flask and re-heated for a further period. α_{5461} fell from $+6{\cdot}86°$ to 0° during 35 hr. By this method values for the times were subject to a small but cumulative error since racemisation would be continuing for short periods during the heating and cooling of the solution. The straight line of the log plot and the constancy of k showed that this error was small: k, $3{\cdot}18$ ($\pm 0{\cdot}01$) $\times 10^{-3}$ min.$^{-1}$; half-life, 218 $\pm$ 1 min.

(*d*) The rate of racemisation in boiling ethylbenzene solution was determined in a similar way. The solution (25 c.c.) contained 0·1419 g. of the (−)-compound and α_{5461} changed from $-17{\cdot}47°$ to 0° during 109 min. Owing to the higher b. p. of this solvent, errors in the values for the times were greater than in the previous experiment: k, $5{\cdot}3$ ($\pm 0{\cdot}2$) $\times 10^{-3}$ min.$^{-1}$; half-life, 13 $\pm$ 1 min.

The values of k obtained in experiments (*c*) and (*d*) give a value for the activation energy of about 34 kcal./mole.

(±)-2 : 7-*Dihydrodinaphtho*(2′ : 1′-3 : 4)(1″ : 2″-5 : 6)*azepinium*-1-spiro-1‴-*piperidinium Bromide*.—Piperidine (1·9 g., 2·2 mols.) in benzene was added to a warm benzene solution of (±)-2 : 2′-bisbromomethyl-1 : 1′-dinaphthyl (4·4 g., 1 mol.). After ½ hr. the benzene was decanted and the residual gum crystallised from water, in which it was sparingly soluble. The *bromide* (3·75 g.) was obtained as hair-like needles, melting at *ca.* 250° to an opaque liquid (Found: C, 69·1; H, 6·4; Br, 16·95. $C_{27}H_{26}NBr,1{\cdot}5H_2O$ requires C, 68·8; H, 6·2; Br, 16·95%). The *picrate*, crystallised from acetone or ethanol, had m. p. 276—277° (block) (Found: C, 65·8; H, 4·8; N, 9·4. $C_{33}H_{28}O_7N_4$ requires C, 66·9; H, 4·8; N, 9·5%).

(+)-2 : 7-*Dihydrodinaphtho*(2′ : 1′-3 : 4)(1″ : 2″-5 : 6)*azepinium*-1-spiro-1‴-*piperidinium Bromide* (VI).—Similar treatment of (−)-2 : 2′-bisbromomethyl-1 : 1′-dinaphthyl (1·1 g.) gave the (+)-quaternary *bromide*, which crystallised from water in hexagonal plates, melting at *ca.* 237° to an opaque liquid (Found: C, 67·0; H, 6·5; Br, 16·6. $C_{27}H_{26}NBr,2H_2O$ requires C, 67·5; H, 6·3; Br, 16·6%), $[\alpha]^{20}_{5461}$ +306·5°, $[\alpha]^{20}_{5791}$ +268·8° (*c*, 1·088 in EtOH). The (+)-compound was much more soluble in water than the racemic compound. The *picrate* crystallised from ethanol in plates, m. p. 222° (Found: C, 65·3; H, 4·8; N, 9·5%). (The low carbon analysis for this and for the racemic compound must result from partial solvation. Insufficient material was available for a quantitative investigation.)

Racemisation of the (+)-*Bromide*.—A solution of the (+)-bromide (0·1868 g.) in ethylene glycol (20 c.c.) was heated quickly to 172° and then transferred to a heating mantle, pre-set so that the temperature of the solution remained at 172°. At suitable intervals the racemisation was stopped by rapid external cooling and polarimetric readings were taken at room temperature. α_{5791} fell from $+5{\cdot}04°$ to $+3{\cdot}98°$ during 8½ hr. but after this it was no longer possible to make polarimetric readings of the solution. The results indicated $k \sim 4{\cdot}5 \times 10^{-4}$ min.$^{-1}$, and half-life ~26 hr. The solution was treated with aqueous picric acid. The precipitated picrate was extracted three times with ethanol (in which the racemic picrate is sparingly soluble). The first extract deposited the optically active picrate, m. p. 221°, mixed m. p. 222°. The third extract deposited the racemic picrate, m. p. 275—276° (block), mixed m. p. 276—277° (block).

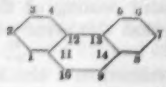
(±)-1 : 1-*Diallyl*-2 : 7-*dihydrodinaphtho*(2′ : 1′-3 : 4)(1″ : 2″-5 : 6)*azepinium Bromide*.—(±)-2 : 2′-Bisbromomethyl-1 : 1′-dinaphthyl and diallylamine were allowed to react together in warm benzene solution during several hours. The solid *bromide* which separated was collected; it crystallised from water in flattened needles, m. p. *ca.* 135° (decomp.) (Found: C, 68·3; H, 6·2; Br, 16·3. $C_{33}H_{36}NBr,2H_2O$ requires C, 68·3; H, 6·1; Br, 16·2%). On attempted recrystallisation from water it separated in very fine needles which formed a gel with the solvent.

(+)-1 : 1-*Diallyl*-2 : 7-*dihydrodinaphtho*(2′ : 1′-3 : 4)(1″ : 2″-5 : 6)*azepinium Iodide* (VII).—The interaction of (−)-2 : 2′-bisbromomethyl-1 : 1′-dinaphthyl and diallylamine in warm benzene solution gave a gum which became crystalline on treatment with water but on attempted recrystallisation from water gave a gel. It was dissolved in hot water and treated with aqueous potassium iodide. The quaternary *iodide* separated and crystallised from dilute aqueous ethanol in plates, m. p. *ca.* 115° (decomp.) (Found: C, 62·2; H, 5·6; I, 23·6. $C_{33}H_{36}NI,2H_2O$ requires C, 62·3; H, 5·6; I, 23·5%), $[\alpha]^{20}_{5461}$ +205·3°, $[\alpha]^{20}_{5791}$ +182·2° (*c*, 1·062 in EtOH).

Appendix (by K. E. Howlett)

In the racemisation of an optically active dihydrophenanthrene, the molecules will probably pass through a planar transition state and the activation energy for the rearrangement will therefore be similar in magnitude to the difference in energy between the

equilibrium state and the planar configuration. Although the strain of the transition state would undoubtedly be spread over the whole molecule, it is reasonable to assume that the benzenoid rings involve more rigid bonds than the bridge links. Also it seems unlikely that the strain can be relieved by deformation of the 4–12–13 and 5–13–12 angles in the plane of the transition state because this would bring the 4- and the 5-hydrogen atom into even closer proximity. Therefore, in order to make a first approximation to the potential-energy difference between initial and transition states, one need only consider bond-bending effects of the carbon skeleton of the bridge at the 11-, 14-, 9-, and 10-positions, together with a compression of the 9—10 carbon–carbon bond.



Certain other activation energy increments may be noted. Whilst the bridge hydrogen atoms experience a part of the ethane energy barrier in passing the eclipsed position, the 4- and the 5-hydrogen atom will suffer half the repulsive forces experienced for an equal twisting motion in diphenyl, and further the coplanarity of the benzenoid rings in the transition state implies a gain in delocalisation energy. These effects, however, are probably small for the low angle of rotation necessary, and moreover the last acts in the opposite sense to the others.

If the vibrational motion of the atoms is assumed to be simple harmonic, *i.e.*, the variation of potential energy with oscillation is of the form :

$$V = V_0 + \tfrac{1}{2}\, k_r \Delta r^2 + \tfrac{1}{2}\, k\, \Delta\theta^2$$

(where V_0 is the potential energy of the equilibrium state of the molecule, k_r and k_θ are respectively bond-stretching and bond-bending constants, and Δr and $\Delta\theta$ are the respective deformations), then the energy barrier to be surmounted may be calculated if the force constants are known. In the calculations described here, the <CCC bending constant is assumed to be $0{\cdot}5 \times 10^{-11}$ dyne-cm./radian^2 (cf. Crawford and Brinkley, *J. Chem. Phys.*, 1941, **9**, 69) and the C–C stretching constant 5×10^5 dyne/cm. (cf. Linnett, *Quart. Rev.*, 1947, **1**, 85). The potential energies of a number of planar configurations have been calculated on the assumptions that in the equilibrium state the bond lengths 12–13, 11–12, 10–11, and 9–10 are respectively 1·50, 1·40, 1·54, and 1·54 Å, whilst the appropriate inter-bond angles are 120° and 109° 28′. The results are set out in tabular form.

θ	ϕ	r (9–10) (Å)	V_θ (cal.)	V_ϕ (cal.)	V_r (cal.)	Total energy (cal.)
120°	120°	1·360	0	2430	23,310	25,740
122	118	1·454	90	1600	5,320	7,010
123	117	1·502	200	1250	1,040	2,490
124	116	1·550	350	950	70	1,370
125	115	1·598	550	670	2,420	3,640
126	114	1·647	800	450	8,260	9,510

θ and ϕ refer to the angles 10–11–12 and 9–10–11 respectively.

The lowest energy pass between the antipodal equilibrium configurations of dihydrophenanthrene is about 1·4 kcal./mole above the ground state. It seems, therefore, that the simple dihydrophenanthrene is likely to be configurationally too unstable to permit of optical resolution. Thus, for example, this energy barrier is similar in magnitude to those separating rotational isomers which are not isolable as chemically distinct species (cf. Pitzer, *J. Amer. Chem. Soc.*, 1948, **70**, 2140). Even the barrier of 10 kcal./mole thought to separate the boat and the chair form of *cyclo*hexane (Shoppee, *J.*, 1946, 1138) is insufficient to allow of chemical separation. In fact 15—18 kcal./mole is probably a lower limit for an energy barrier which would enable optically active species to be studied by observing a mutarotational change (cf. Jamison and Turner, *J.*, 1938, 1652, who found the mutarotation of the cinchonidine salt of *N*-benzoyl-4 : 6 : 4′-tribromodiphenylamine-2-carboxylic acid to have a half-life of 15 min. at 17·6° and an activation energy for the mutarotation process of 21 kcal./mole).

The calculation indicates, incidentally, that the 9–10 bond is probably shortened by only about 0·01 Å in the transition state whilst the original tetrahedral angles of the bridge are opened to about 116°. Thus *a posteriori* it can be appreciated (*a*) that the

assumption of simple harmonic motion is unlikely to be seriously in error for a bond oscillation of the order of 0·1 radian, and (*b*) that neglect of compression in the other bridge links (which would be even less than in the 9–10 bond) is justified.

The application of a calculation, similar to that employed for dihydrophenanthrene, to a diphenyl derivative with a seven-membered carbocyclic bridging ring has been attempted. By assuming as a further approximation in this case that the planar transition state causes no compressional effects in the bridge bonds, the activation energy for racemisation is estimated to be 19 kcal./mole. This figure is in qualitative agreement with the known optical stability of the azepinium salt (V).

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Preparation of Some Bisaminoaryl Sulphones.

By M. BALASUBRAMANIAN and V. BALIAH.

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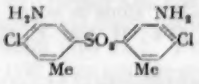
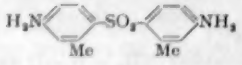
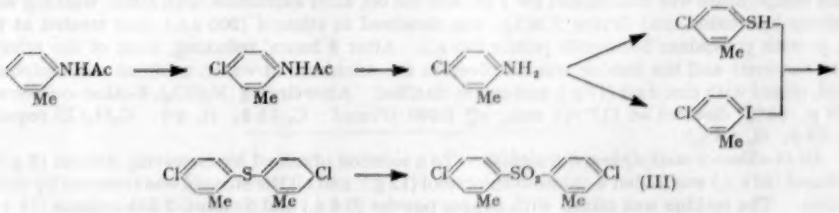
Aceto-*p*- and -*m*-toluidide condense with thionyl chloride in the presence of aluminium chloride to give di-(5-acetamido-4-chloro-2-methylphenyl) and di-(4-acetamido-2-methylphenyl) sulphoxide respectively. The corresponding acetamido-sulphones and amino-sulphones have been prepared.

THE high antibacterial activity of di-(4-aminophenyl) sulphone prompted us to prepare some analogous amino-sulphones. Reaction of acetanilide with thionyl chloride in the presence of aluminium chloride yields di-(*p*-acetamidophenyl) sulphoxide which on oxidation and subsequent deacetylation gives di-(*p*-aminophenyl) sulphone (Sugaswa and Sakurai, *J. Pharm. Soc. Japan*, 1940, **60**, 22). We investigated a similar reaction with the three isomeric acetotoluidides. Aceto-*o*-toluidide failed to undergo the reaction. Aceto-*p*-

(I) 

 (II)

and -*m*-toluidide gave sulphoxides which were oxidised to the corresponding sulphones and then hydrolysed to the amino-sulphones (I) and (II) respectively, nuclear chlorination occurring in the former case. The structures (I) and (II) were established as follows: Deamination of the sulphone (I) gave di-(4-chloro-2-methylphenyl) sulphone (III) which



(III)

was synthesised unequivocally as shown. Replacement of the amino-groups in the sulphone (II) by chlorine gave the dichloro-sulphone (III) which was also obtained by oxidising the sulphoxide formed on condensation of *m*-chlorotoluene with thionyl chloride. Deamination of (II) gave di-*o*-tolyl sulphone identical with a sample synthesised unequivocally from *o*-thiocresol and *o*-iodotoluene. Purgotti (*Gazzetta*, 1890, **20**, 31) reported

the melting point of di-*o*-tolyl sulphone as 134—135° whereas we found it to melt at 104·5—105·5°. Purgotti obtained his compound by the oxidation of the supposed di-*o*-tolyl sulphide boiling at 285°. The authenticity of his sulphide is questionable in view of the fact that di-*o*-tolyl sulphide melts at 64° (cf. Zeiser, *Ber.*, 1895, **28**, 1674; Mauthner, *Ber.*, 1906, **39**, 3595).

Experimental

Thionyl chloride was distilled, first, from quinoline and then from linseed oil; the fraction of b. p. 76—78° was used.

Di-(5-acetamido-4-chloro-2-methylphenyl) Sulphoxide.—Thionyl chloride (59·5 g.) in carbon disulphide (50 c.c.) was added dropwise during 45 min. to a well-stirred mixture of aceto-*p*-toluidide (74·5 g.), finely powdered aluminium chloride (100 g.), and carbon disulphide (500 c.c.) kept at 40—45°. The mixture was then stirred for 4 hr. at 50°; after cooling, the carbon disulphide layer was decanted from the insoluble, viscous sulphoxide–aluminium chloride complex which was decomposed by crushed ice. Next morning the solid was filtered off, agitated with a mixture of acetone (20 c.c.) and ether (100 c.c.), collected, and washed successively with ether and water. The *sulphoxide* (45 g., 44% based on aceto-*p*-toluidide) melted at 208·5—210° (from ethanol) (Found: C, 52·5; H, 4·4; $C_{16}H_{16}O_3N_2Cl_2S$ requires C, 52·3; H, 4·4%).

There was no reaction under the conditions used for aceto-*m*-toluidide.

Di-(5-acetamido-4-chloro-2-methylphenyl) Sulphone.—A hot solution of the above sulphoxide (10 g.) in acetic acid (150 c.c.) was mixed with hydrogen peroxide (30%; 6 c.c.), left overnight, heated on a steam-bath for 1 hr., and diluted with water. The precipitated *sulphone* formed needles (6·2 g., 60%), m. p. 278—280° (decomp.), from acetic acid (Found: C, 50·5; H, 4·3; S, 7·4. $C_{16}H_{16}O_4N_2Cl_2S$ requires C, 50·4; H, 4·2; S, 7·5%).

Di-(5-amino-4-chloro-2-methylphenyl) Sulphone (I).—The foregoing acetamido-sulphone (6 g.) was hydrolysed by refluxing it with sulphuric acid (30 c.c.) and water (60 c.c.) for 45 min. The *amino-sulphone* formed pale yellow needles (4·6 g., 96%), m. p. 181—182°, from ethanol (Found: C, 48·6; H, 4·0; S, 9·3. $C_{14}H_{14}O_2N_2Cl_2S$ requires C, 48·7; H, 4·1; S, 9·3%).

Deamination of Di-(5-amino-4-chloro-2-methylphenyl) Sulphone.—The amino-sulphone (1 g.) in hydrochloric acid (*d* 1·08; 6 c.c.) was tetrazotised with sodium nitrite (0·52 g.) in water (2 c.c.), and the resulting solution was added to hypophosphorous acid (50%; 6 c.c.) at 0°. Next day, the precipitate formed was extracted with benzene, and the extract, after being washed with a 5% solution of sodium hydroxide and then with water, was evaporated to yield a residue which, after crystallisation from ethanol, melted at 135—137° alone or mixed with *di-(4-chloro-2-methylphenyl) sulphone* prepared as below (Found: C, 53·4; H, 3·6. $C_{14}H_{12}O_2Cl_2S$ requires C, 53·3; H, 3·8%).

4-Chloro-o-toluidine ($NH_2 = 1$).—It was obtained by the hydrolysis of 4-chloroaceto-*o*-toluidide with hydrochloric acid (cf. Reverdin and Crèpieux, *Ber.*, 1900, **33**, 2497), and had b. p. 140°/38 mm.

4-Chloro-o-thiocresol (SH = 1).—4-Chloro-*o*-toluidine (28·3 g.) in hydrochloric acid (*d* 1·08; 126 c.c.) was diazotised with sodium nitrite (15 g.) in water (15 c.c.), and the solution was added in a stream, with stirring, to potassium ethyl xanthate (50 g.) in water (50 c.c.) at 40—45°. This temperature was maintained for 1 hr. and the oil, after extraction with ether, washing with sodium hydroxide, and drying ($CaCl_2$), was dissolved in ethanol (200 c.c.), and treated at the b. p. with potassium hydroxide pellets (65 g.). After 8 hours' refluxing, most of the ethanol was removed and the residue was dissolved in the minimum of water, acidified with sulphuric acid, mixed with zinc dust (10 g.), and steam-distilled. After drying ($MgSO_4$), *4-chloro-o-thiocresol* (28 g., 88%) distilled at 117°/21 mm., n_D^{28} 1·590 (Found: C, 53·2; H, 4·7. C_7H_7ClS requires C, 53·0; H, 4·4%).

Di-(4-chloro-2-methylphenyl) Sulphide.—To a solution obtained by dissolving sodium (2 g.) in ethanol (40 c.c.) was added 4-chloro-*o*-thiocresol (12 g.), and all the ethanol was removed by distillation. The residue was mixed with copper powder (0·6 g.) and 5-chloro-2-iodotoluene (19·1 g.) (Beilstein and Kuhlberg, *Annalen*, 1870, **156**, 82), heated at 240—245° for 3½ hr., cooled, mixed with ethanol (60 c.c.), and strongly acidified with sulphuric acid (1 : 1). After the addition of zinc dust (2 g.), the mixture was steam-distilled to remove unchanged reactants, and the residue on ether-extraction and drying ($CaCl_2$) gave the *sulphide* (15·5 g., 72%), b. p. 213—215°/17 mm., n_D^{20} 1·6295 (Found: C, 59·3; H, 4·5. $C_{14}H_{12}Cl_2S$ requires C, 59·4; H, 4·2%).

Di-(4-chloro-2-methylphenyl) Sulphone (III).—The foregoing sulphide (5 g.) in hot acetic

acid (100 c.c.) was oxidised with 5% potassium permanganate solution (excess). The *sulphone* (5·2 g., 93%) crystallised as needles, m. p. 139—140°, from ethanol or light petroleum (b. p. 140—150°) (Found : C, 53·0; H, 4·0%).

Di-(4-acetamido-2-methylphenyl) Sulphoxide.—With aceto-*m*-toluidide (14·9 g.), aluminium chloride (26·6 g.), carbon disulphide (150 c.c.), and thionyl chloride (6 g. in 10 c.c. of carbon disulphide) the reaction was effected as in the earlier condensation, except that the refluxing was stopped 2 hr. after the addition of thionyl chloride. The *sulphoxide* (14 g., 81%) melted at 209—211° (from acetone–water) (Found : C, 62·7; H, 6·05; S, 9·3. $C_{18}H_{20}O_3N_2S$ requires C, 62·8; H, 5·8; S, 9·3%).

Di-(4-acetamido-2-methylphenyl) Sulphone.—The above sulphoxide (9 g.) in hot acetic acid (90 c.c.) was oxidised with potassium permanganate (5·4 g.) in water (160 c.c.). The *acetamido-sulphone* (7 g., 74%) melted at 243—244° (from acetic acid) (Found : C, 59·8; H, 5·5. $C_{18}H_{20}O_4N_2S$ requires C, 60·0; H, 5·6%).

Di-(4-amino-2-methylphenyl) Sulphone (II).—This *compound*, obtained in 91% yield by the hydrolysis of the acetamido-sulphone with hydrochloric acid (1 : 1), crystallised from ethanol as pale yellow needles, m. p. 280° (decomp.) (Found : C, 60·6; H, 5·9; S, 11·2. $C_{14}H_{16}O_2N_2S$ requires C, 60·9; H, 5·8; S, 11·6%).

Deamination. The procedure used for the deamination of (I) was followed. The product after crystallisation from methanol melted at 103—104·5°, alone or mixed with di-*o*-tolyl sulphone prepared as below (Found : C, 68·0; H, 5·8. $C_{14}H_{14}O_2S$ requires C, 68·3; H, 5·7%).

Di-o-tolyl Sulphone.—Di-*o*-tolyl sulphide (3 g.), m. p. 64—64·5° (Mauthner, *loc. cit.*), was oxidised in acetic acid (100 c.c.) with 5% potassium permanganate solution. The *sulphone* (3·2 g., 94%) melted at 104·5—105·5° (from methanol) (Found : C, 68·6; H, 5·6; S, 13·3. $C_{14}H_{14}O_2S$ requires S, 13·0%).

Di-(4-chloro-2-methylphenyl) Sulphone.—The tetrazo-solution obtained from the amino-sulphone (II) (1 g.) was mixed with a solution of cuprous chloride [prepared from copper sulphate (4 g.) and sodium chloride (1·1 g.)] in hydrochloric acid (4 c.c.), then heated on a water-bath until the evolution of nitrogen ceased, and the precipitate formed was collected, washed with alkali and water, and extracted with boiling light petroleum (b. p. 140—150°). The residue, after evaporation of the solvent and crystallisation from ethanol–water, yielded di-(4-chloro-2-methylphenyl) sulphone (0·4 g.), m. p. 138—139°, undepressed on admixture with the synthetic sample (Found : C, 53·2; H, 4·0%).

Di-(4-chloro-2-methylphenyl) Sulphoxide.—Thionyl chloride (10 g.) was added during 45 min. to *m*-chlorotoluene (10 g.), aluminium chloride (20 g.), and carbon disulphide (100 c.c.); the whole was heated for a further 3 hr. and then poured into ice-water. After removal of the carbon disulphide, the product was steam-distilled to remove unchanged *m*-chlorotoluene and extracted with boiling methanol (150 c.c.). Evaporation of the solvent gave the *sulphoxide* (6·5 g., 57%), m. p. 102—103° (from acetone–water) (Found, after drying at 56° under reduced pressure : C, 53·2; H, 4·6. $C_{14}H_{12}OCl_2S,H_2O$ requires C, 53·0; H, 4·4%).

Oxidation of the sulphoxide with potassium permanganate in acetic acid yielded di-(4-chloro-2-methylphenyl) sulphone in 87% yield.

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X-Ray Studies in the Caryophyllene Series. The Chloride and Bromide from β-Caryophyllene Alcohol.

By J. Monteath Robertson and G. Todd.

[Reprint Order No. 5891.]

A complete *X*-ray structure determination of the chloride from β-caryophyllene alcohol is described, based on an interpretation of the two principal electron-density projections. Partial phase determination was achieved by the isomorphous replacement method, making use of the bromide and chloride. The complete structure was built up by successive approximations from this basis, as recognisable fragments of the molecule became clear. The space group is $D_2^4 - P2_12_12_1$ and there are four molecules per unit cell.

The structure obtained is in complete agreement with that deduced from chemical evidence by Barton, Bruun, and Lindsey, and enables further stereochemical points to be established regarding the nature of the ring fusions and the shapes of the rings. It also supports the chemical structures assigned to β-caryophyllene alcohol and β-caryophyllene itself.

The *X*-ray studies described in this paper commenced in 1950, when the constitution of β-caryophyllene and its derivatives was still in considerable doubt. Since that time infrared spectroscopic work (Šorm, Dolejš, and Plíva, *Coll. Czech. Chem. Comm.*, 1950, **15**, 186) and chemical work (Barton and Lindsey, *J.*, 1951, 2988; Barton, Bruun, and Lindsey, *J.*, 1952, 2210; Aebi, Barton, and Lindsey, *J.*, 1953, 3124) have cleared up the doubtful points, and the conclusions are in agreement with our *X*-ray work, on which a preliminary note has been published (Robertson and Todd, *Chem. and Ind.*, 1953, 437).

The isomorphous-replacement method of phase determination (Robertson, *J.*, 1935, 615; 1936, 1195) offers the best chance of success with a structure of this degree of complexity. It proved difficult to prepare suitable derivatives from β-caryophyllene itself; but the chloride and bromide of β-caryophyllene alcohol (Wallach and Walker, *Annalen*, 1892, **271**, 285; Tuttle, *N. Jahrb. Min., Geol. u.s.w.*, 1894—95, Beil.-Bd., **9**, 451; *Z. Krist.*, 1897, **27**, 526) are nicely crystalline and known to be isomorphous. These derivatives proved suitable for a complete structure determination of the tricyclic molecule, and the results, taken in conjunction with the chemical evidence of Barton, Bruun, and Lindsey (*loc. cit.*), support the constitution which these authors have assigned to β-caryophyllene.

Crystal Data.—β-Caryophyllene alcohol chloride, $C_{15}H_{25}Cl$; *M*, 240·8; m. p. 62—63°; *d*, calc. 1·115, found 1·135. Orthorhombic, $a = 8{\cdot}27 \pm 0{\cdot}04$, $b = 10{\cdot}54 \pm 0{\cdot}05$, $c = 16{\cdot}47 \pm 0{\cdot}08$ Å. Absent spectra, ($h00$) when h is odd, ($0k0$) when k is odd, ($00l$) when l is odd. Space group, $D_2^4 - P2_12_12_1$. Four molecules per unit cell. No molecular symmetry required. Volume of the unit cell = 1436 Å^3. Absorption coefficient for *X*-rays ($\lambda = 1{\cdot}54$ Å) $\mu = 22{\cdot}2$ per cm. Total number of electrons per unit cell = F(000) = 528.

β-Caryophyllene alcohol bromide, $C_{15}H_{25}Br$; *M*, 285·3; m. p. 60—61°; *d*, calc. 1·292, found 1·293. Orthorhombic, $a = 8{\cdot}35 \pm 0{\cdot}04$, $b = 10{\cdot}75 \pm 0{\cdot}05$, $c = 16{\cdot}41 \pm 0{\cdot}08$ Å. Absent spectra, ($h00$) when h is odd, ($0k0$) when k is odd, ($00l$) when l is odd. Space group, $D_2^4 - P2_12_12_1$. Four molecules per unit cell. No molecular symmetry required. Volume of the unit cell = 1467 Å^3. Absorption coefficient for *X*-rays ($\lambda = 1{\cdot}54$) $\mu = 38{\cdot}6$ per cm. Total number of electrons per unit cell = F(000) = 600.

For both substances the crystals were usually tabular with (001) well developed. Occasionally, small prismatic rhombs were obtained, elongated along *c*. The crystals have been described by Tuttle (*loc. cit.*) and his figures for the axial ratios are in very good agreement with our measurements.

Structure Analysis. Patterson Syntheses.—Our work on this structure has been confined to a study of the three axial zones of reflections from each crystal, and the corresponding two-dimensional projections. There are naturally some difficulties in resolving all the atoms by these methods; but although the accuracy finally attained is not very

high (about $\pm 0{\cdot}1$ Å in bond lengths) it is sufficient to solve the structure completely as regards the configuration of the molecule.

There is no centre of symmetry in the space group $P2_12_12_1$, the elements being three mutually perpendicular sets of non-intersecting screw axes. The general origin ("International Tables for *X*-Ray Crystallography," 1952, Kynoch Press, Birmingham) is equidistant from three pairs of these axes. All co-ordinates given in this paper are referred to this origin. The projections along the three principal axes are centrosymmetrical, however, at the points where the screw axes intersect the projection planes, and it is convenient to use these points as origins for the calculation of structure factors (Tables 4 and 5). These origins are not spatially coincident, and the ones chosen are related to the general origin as follows: zone (0*kl*) origin at $(\frac{1}{4}0\frac{1}{4})$, zone (*h*0*l*) origin at $(\frac{1}{4}0\frac{1}{2})$, zone (*hk*0) origin at $(\frac{1}{2}\frac{1}{4}\frac{1}{4})$.

The first step in the analysis is the determination of the positions of the replaceable halogen atoms, of which there are four in the unit cell. This was accomplished without difficulty by an application of the Patterson method. Fig. 1 shows a portion of the vector map obtained for the *a*-axis projection of β-caryophyllene bromide. Large peaks

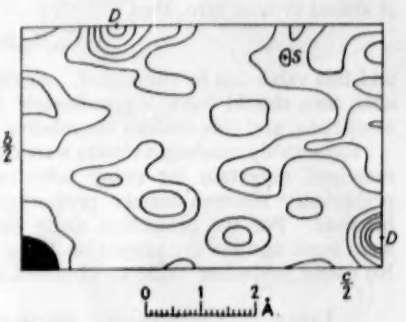


FIG. 1. *Asymmetric portion of Patterson projection along a axis for β-caryophyllene bromide.*

such as *D*, at $y = \frac{1}{2}$ and $z = \frac{1}{4}$, are formed by the superposition of two equivalent vectors related to each other by the centre of symmetry in this projection, whereas a peak such as *S* is due to a unique vector crossing the centre of symmetry.

Similar syntheses were applied to the (*h*0*l*) and (*hk*0) data. Solution of the vector sets was effected without difficulty and the co-ordinates obtained for the bromine atom are given in Table 1.

TABLE 1.

Zone	Bromine co-ordinates *x/a*	*y/b*	*z/c*
0*kl*	—	0·218	0·567
*h*0*l*	0·290	—	0·563
*hk*0	0·292	0·218	—
Average	0·291	0·218	0·565

The position of the chlorine atom in the chloride was found to be closely similar, and the co-ordinates obtained, after the structure had been fully refined, are included in Table 2. The bromide was utilized for phase determination, and a number of preliminary projections of the structure were obtained which established its close isomorphism with the chloride. All the later work on the refinement of the structure was, however, carried out on the chloride, and we do not feel justified in reporting any further co-ordinates for the bromide; in the preliminary studies they were not found to differ significantly from those obtained for the chloride.

Isomorphous-replacement Method and Preliminary Structure.—The positions of the halogen atoms having been determined, it was possible to calculate their contribution to each reflection and assess their effectiveness for phase determination. If we assume strict isomorphism, then for any plane we can write the following relation between the structure factors F for the bromide and chloride:

$$F(C_{15}H_{25}Br) - F(C_{15}H_{25}Cl) = F(Br) - F(Cl) = \Delta F$$

The contributions from the atoms other than halogen cancel out, and the difference, ΔF, may be calculated from the atomic scattering curves (f) for bromine and chlorine, and the purely geometrical factor s which depends upon their known co-ordinates :

$$\Delta F = s(f_{Br} - f_{Cl})$$

If the value of ΔF is large enough to be significant with the accuracy available, then it can be used to determine the signs of the two structure factors $F(C_{15}H_{25}Br)$ and $F(C_{15}H_{25}Cl)$ without ambiguity.

The difficulties which attend the practical application of this method are mainly concerned with making reliable absolute determinations of the F values, and with uncertainties regarding the strictness of the isomorphism. In this investigation we did not make any direct absolute measurements. Instead, the relative F values were put on an approximately absolute scale by making use of various modifications of Wilson's statistical methods (*Nature*, **1942**, **150**, 152). A check on these results was made for certain special planes, *e.g.*, when the reflection from one of the isomorphs, say the chloride, is absent or near zero, then

$$F(C_{15}H_{25}Br) - 0 = s(f_{Br} - f_{Cl})$$

and this value can be calculated. Again, reflections for which the halogen contribution is near zero should have approximately the same absolute value in the case of the two isomorphs, and this enables the relative scaling factor to be determined.

Reasonably consistent results were obtained by these methods, but phase determination remained uncertain for many reflections with small halogen contribution. However, preliminary electron-density projections of the structure were now prepared for the bromide. For the projection along the a axis, 80 structure factors in the ($0kl$) series were used, and for the projection along the b axis, 73 structure factors in the ($h0l$) series. No useful projection could be obtained along the c axis.

TABLE 2. *Co-ordinates. Origin equidistant from three pairs of non-intersecting screw axes.*

Atom	x/a	y/b	z/c	X(Å)	Y(Å)	Z(Å)
Cl	0·285	0·207	0·564	2·36	2·18	9·29
C(1)	0·411	0·068	0·557	3·40	0·72	9·18
C(2)	0·438	0·017	0·467	3·62	0·18	7·70
C(3)	0·323	0·053	0·395	2·67	0·56	6·51
C(4)	0·475	0·051	0·341	3·93	0·54	5·62
C(4′)	0·466	0·165	0·276	3·85	1·74	4·54
C(4″)	0·525	−0·080	0·296	4·34	−0·84	4·88
C(5)	0·577	0·090	0·419	4·77	0·95	6·90
C(6)	0·744	0·038	0·438	6·15	0·40	7·22
C(7)	0·744	−0·065	0·511	6·15	−0·68	8·42
C(8)	0·710	−0·004	0·598	5·87	−0·04	9·85
C(8′)	0·863	0·038	0·638	7·14	0·40	10·51
C(9)	0·632	−0·103	0·655	5·23	−1·09	10·79
C(10)	0·468	−0·139	0·624	3·87	−1·46	10·28
C(11)	0·345	−0·023	0·614	2·85	−0·24	10·12
C(12)	0·590	0·110	0·590	4·88	1·16	9·72

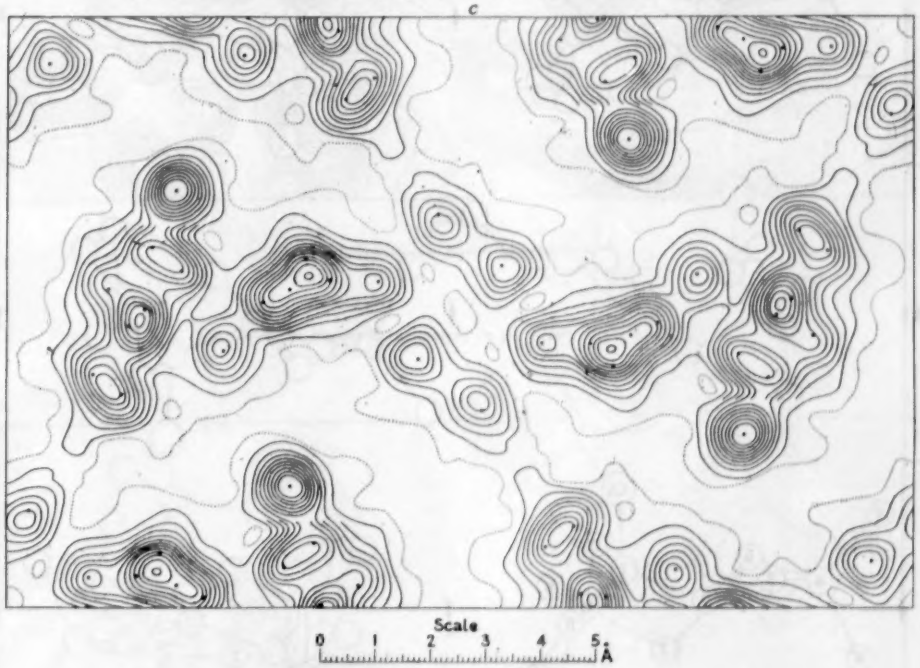
The interpretation of these preliminary maps proved difficult, as there were several unresolved regions on both projections.* At this date (1950) one of the few features of the β-caryophyllene structure that had been definitely established from chemical evidence was the existence of a four-membered ring with a *gem*-dimethyl group (Rydon, *J.*, 1936, 593; 1937, 1340). These atoms could be located on the two projections with some certainty, but attempts to build the complete structure from this basis were at first unsuccessful. It was realised, however, that, although the chemical structure of β-caryophyllene was in doubt, all the possibilities indicated the presence of a six-membered ring in the tricyclic alcohol and its derivatives It was also clear that with the position assigned to the *cyclo*butane ring in the two projections, the *cyclo*hexane ring would be badly resolved,

* These preliminary electron-density projections have been reproduced in the Third Henderson Memorial Lecture (*Roy. Inst. Chem. Monographs*, 1954, No. 6).

and in the *a*-axis projection in particular would provide only an end-on view. This interpretation of one of the unresolved regions enabled a trial structure to be set up, and structure-factor calculations on this basis led to an immediate improvement in the agreements obtained with the observed values.

From this point onwards the refinement of the structure proceeded steadily. All the later work was based on the intensities obtained from the chloride, which could be measured more accurately than those of the bromide, owing to the smaller absorption coefficient. The electron-density maps were also easier to interpret because diffraction effects from the heavy atom were less serious. In the later refinement work considerable use was made of the method of difference synthesis. At one stage these methods showed that the methyl group, $C_{(8')}$, had been wrongly placed, and after correction the structure-factor

FIG. 2. *Electron-density projection on* (100). *Contours at intervals of* 1 eÅ^{-2}, *except on chlorine, with one-electron line dotted. This projection is based on* 115 (0*kl*) *structure factors.*



agreements showed further large improvements. In all, some 40 two-dimensional syntheses were made in the course of this work.

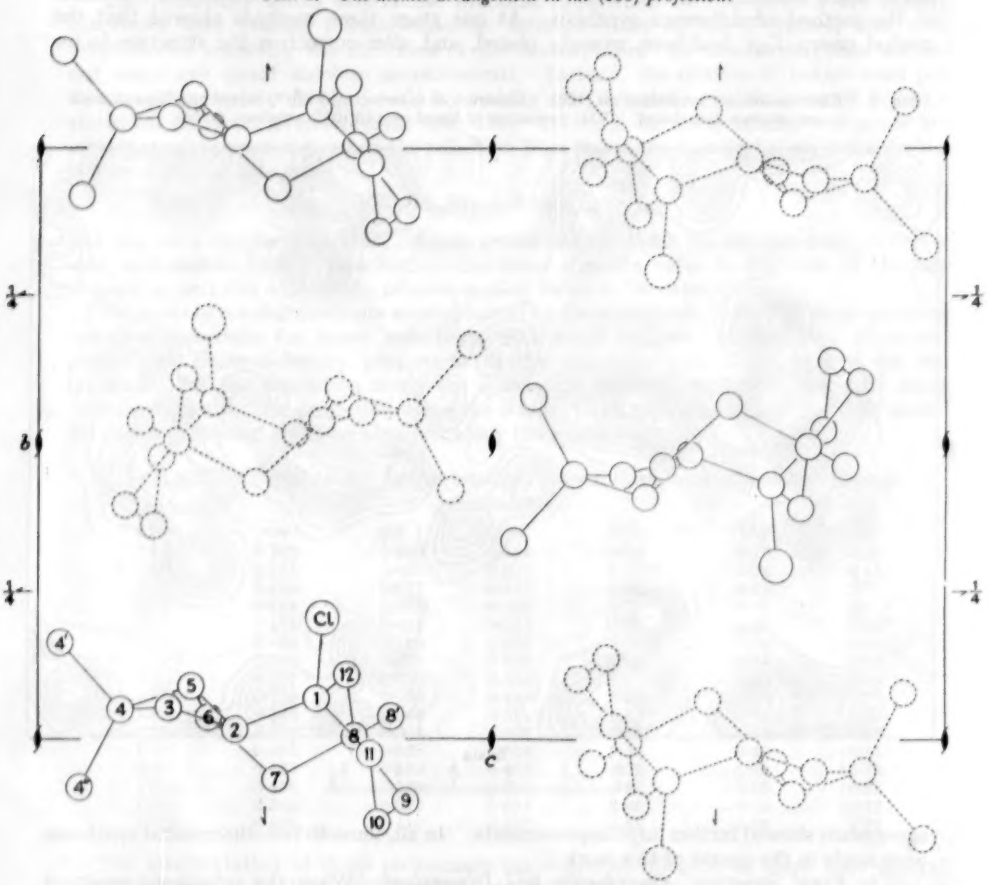
The Final Structure. Co-ordinates and Dimensions.—When the refinement work on the chloride had been completed, the final discrepancies between calculated and observed structure factors in the different zones, expressed as percentages of the total of the measured structure factors in the usual way, were as follows: (0*kl*) zone, 15·7%; (*h*0*l*) zone, 12·3%; (*hk*0) zone, 24·0%; overall, 17·5%. Electron-density maps were not prepared for the (*hk*0) zone, but difference-synthesis refinements were carried out. Hydrogen-atom contributions were not included in any of the structure factor calculations (Table 4). The discrepancy figures show that a reasonably accurate picture of the structure has now been obtained.

The final electron-density projections along the *a* and *b* axes are shown in Figs. 2 and 4, and corresponding views of the atomic positions in Figs. 3 and 5. Reasonably good

resolution of most of the carbon atoms is achieved in Fig. 4, but only a few are separately resolved in Fig. 2. It is clear, however, that the plotted positions of the atoms in Fig. 3 and Fig. 5 explain all the features of the electron density maps. A more detailed picture of the structure could only be obtained from a full three-dimensional analysis.

The co-ordinates of the atoms were individually adjusted from a study of a large number of successive difference syntheses on the three principal zones, and very good agreement was finally obtained for the co-ordinate common to any two zones. After

FIG. 3. *The atomic arrangement in the* (100) *projection.*



averaging, the final values are given in Table 2, with the atoms numbered as shown in the diagrams.

The interatomic distances calculated from these co-ordinates are given in Table 3. All the carbon–carbon bond lengths are found to lie in the range 1·45—1·64 Å, with a mean

TABLE 3. *Interatomic distances* (Å).

C(1)–Cl = 1·79	C(2)–C(3) = 1·57	C(5)–C(6) = 1·52	C(8)–C(8′) = 1·50
C(1)–C(12) = 1·64	C(3)–C(4) = 1·54	C(6)–C(7) = 1·61	C(9)–C(10) = 1·50
C(1)–C(11) = 1·45	C(4)–C(5) = 1·59	C(7)–C(8) = 1·59	C(10)–C(11) = 1·60
C(1)–C(2) = 1·59	C(4)–C(4′) = 1·62	C(8)–C(12) = 1·56	
C(2)–C(5) = 1·60	C(4)–C(4″) = 1·62	C(8)–C(9) = 1·55	

FIG. 4. *Electron-density projection on* (010). *Contours at intervals of* 1 eÅ^{-3}, *except on chlorine, with one-electron line dotted. This projection is based on* 84 (*h*0*l*) *structure factors.*

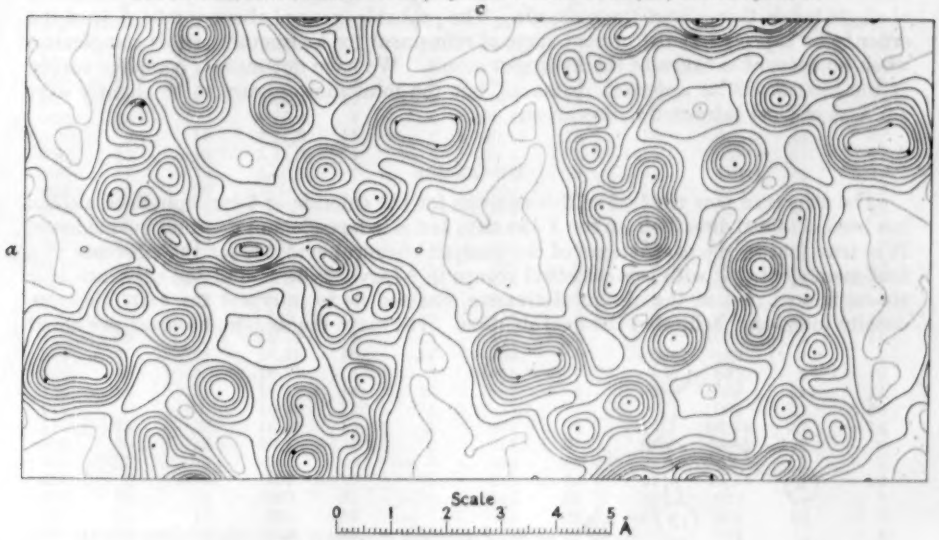
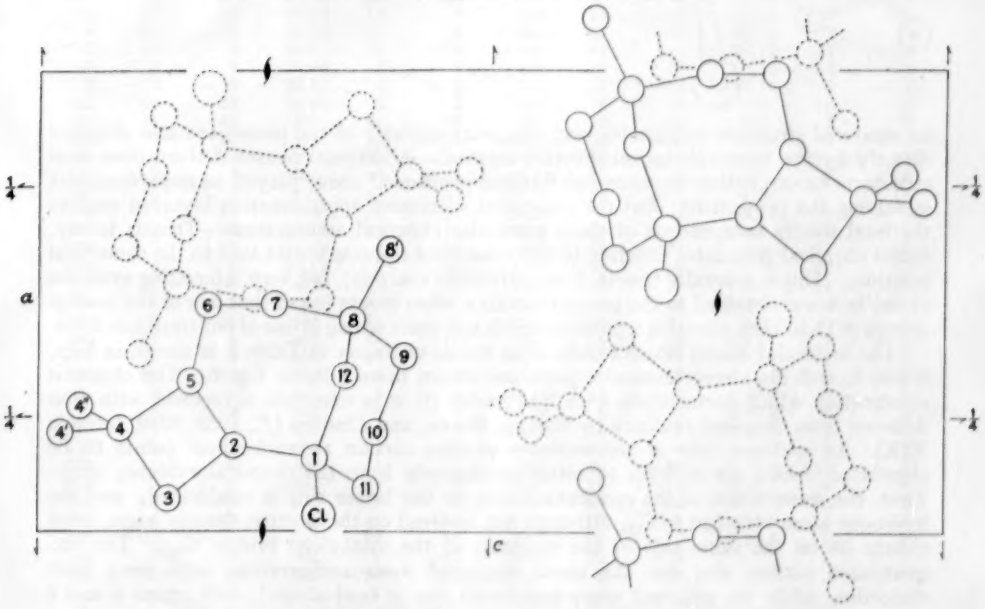


FIG. 5. *The atomic arrangement in the* (010) *projection.*



value of 1·57 Å. If we exclude the bonds from atom C(1), where the co-ordinates are more likely to be inaccurate because of the proximity of the chlorine atom, the carbon–carbon bonds lie in the range 1·50—1·62 Å, and provide clear evidence for the existence of single bonds throughout the molecule. The probable error of about ±0·06 Å is of the order to be expected at the present stage of refinement for a structure of this complexity, when no account is taken of the hydrogen atoms. We have not made a complete survey of the intermolecular approach distances, but the minimum appears to be slightly over 4·0 Å as in most saturated hydrocarbons.

Discussion

The structure now reached in this analysis for the chloride of β-caryophyllene alcohol has been obtained directly from the *X*-ray data and is independent of the chemical evidence. It is true that in the early stages of the analysis chemical evidence for the existence of a four-membered ring with *gem*-dimethyl groups in β-caryophyllene, and the existence of a six-membered ring in the alcohol derivative, enabled us to interpret the early electron-density maps and facilitated the final solution. The maps themselves, however, are based

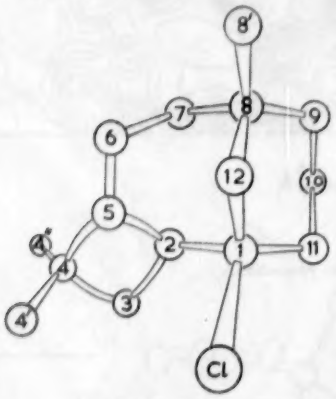


Fig. 6. *Perspective drawing of the β-caryophyllene chloride molecule.*

on *measured* structure amplitudes, and the great majority of the phases are also obtained directly by the isomorphous substitution method. Additional phases derived from trial structures incorporating the chemical features mentioned above played an important part in solving the projections; but the process of successive approximation involved renders the final results independent of these particular chemical assumptions. That is to say, initial chemical postulates differing in quite material respects would lead to the same final solution. This is generally true in *X*-ray structure analysis; but very interesting evidence of the fact was obtained in the present instance when it was found that one of the methyl groups (8′) had been placed in a position which was quite wrong in one of our trial structures.

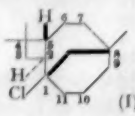
The molecular model which results from the co-ordinates in Table 2 is shown in Figs. 3 and 5, and the stereochemical aspects are shown more fully in Fig. 6. The chemical constitution which corresponds with this model (I) is in complete agreement with that deduced from chemical evidence by Barton, Bruun, and Lindsey (*J.*, 1952, 2210, formula XIX). In addition, the *X*-ray evidence enables certain stereochemical points to be elucidated, which are difficult to settle conclusively from the chemical evidence alone. Thus, the *trans*-fusion of the *cyclo*butane ring to the larger ring is established; and the hydrogen atom attached to $C_{(5)}$, although not resolved on the electron-density maps, must clearly lie on the same side of the molecule as the methylene bridge, $C_{(12)}$. The six-membered carbon ring has the usual staggered *trans*-configuration, with very little distortion, while the adjacent seven-membered ring is boat-shaped, with atoms 5 and 6 *cis* to atom 12. The four-membered ring is somewhat distorted from a planar configuration, as would be expected from the nature of the fusion with the larger ring.

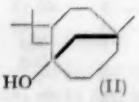
TABLE 4. *Caryophyllene chloride. Measured and calculated values of the structure factor.*

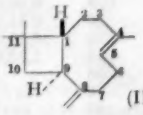
hkl	F (meas.)	F (calc.)	*hkl*	F (meas.)	F (calc.)	*hkl*	F (meas.)	F (calc.)	*hkl*	F (meas.)	F (calc.)
000	—	528	290	10	11	605	10	−11	04,12	7	− 5
200	12	14	490	7	7	606	11	−11	04,14	7	4
400	31	30	790	6	4	607	7	− 8	04,15	7	− 8
600	11	11	2,10,0	10	8	608	13	−15	051	11	−14
020	105[1]	123	6,10,0	7	4	60,11	9	11	052	9	− 5
040	9	18	2,11,0	12	− 8	60,13	10	10	053	21	27
060	15	−10	5,11,0	4	− 4	60,17	2	− 4	054	12	17
080	21	−18	2,12,0	7	8	701	19	−18	055	18	−15
002	87	−96				702	12	−13	056	7	7
004	73	−76	101	—[2]	9	704	6	−12	059	20	22
006	56	57	103	16	15	70,12	7	8	05,10	13	6
008	25	−22	104	47	−49	805	8	−13	05,11	8	− 7
00,10	11	10	105	24	−21	806	8	9	05,12	13	15
00,14	12	−16	106	33	33	807	9	− 9	05,14	13	−10
00,18	7	− 8	107	30	−35	80,11	12	12	05,15	4	− 4
			109	18	−16	902	5	− 8	061	45	−45
110	26	32	10,10	9	11	903	7	− 4	065	11	14
210	41	−38	10,11	16	−16	904	7	−10	066	8	7
310	15	−18	10,12	5	− 7	905	7	− 4	067	8	−10
510	13	15	10,13	14	−10	909	6	5	068	11	13
610	9	− 5	10,14	11	10				069	29	30
710	18	−22	10,17	13	12	011	9	−10	06,11	17	−18
810	10	−10	10,19	4	2	013	64	62	06,12	8	− 9
120	29	−43	201	8	− 5	014	56	−57	06,14	5	7
220	5	−13	202	79	79	015	36	31	06,15	6	9
320	34	21	203	31	−30	016	39	37	072	14	− 7
420	10	16	204	10	− 7	017	22	−26	073	10	− 7
620	8	0	205	17	15	019	10	−13	074	7	4
10,20	5	5	206	31	−29	01,10	24	−26	075	31	33
130	5	−11	208	9	−14	01,12	12	14	077	22	−23
230	25	24	20,11	10	13	01,14	14	−15	078	7	−11
330	33	−19	20,12	7	10	021	62	−62	079	8	5
430	16	17	20,13	20	23	022	29	−28	07,10	5	− 7
530	21	24	20,15	12	9	023	24	22	07,11	12	15
630	20	−26	20,16	12	14	024	47	−45	07,12	9	9
730	11	5	20,17	11	−10	025	54	45	07,13	11	−10
830	8	9	20,18	5	6	026	10	−16	07,15	4	1
10,30	6	− 6	20,19	8	− 5	027	59	−58	07,16	6	− 4
140	24	−23	20,20	3	2	028	25	26	081	11	10
240	44	−53	302	46	−40	029	23	23	082	7	6
340	28	21	303	24	−23	02,10	20	−16	083	6	−12
440	10	10	305	33	−28	02,13	13	−13	085	19	−23
740	7	5	306	40	−34	02,14	10	11	087	9	14
840	6	− 2	307	23	−22	02,16	10	−11	088	10	12
150	17	13	309	10	−14	02,20	5	3	08,15	5	− 5
250	29	−44	30,10	11	11	031	15	7	091	13	−11
550	7	5	30,12	8	10	032	58	−61	092	13	−17
650	8	− 9	30,13	8	10	033	63	−49	093	10	13
750	12	− 8	402	13	10	034	51	39	094	11	14
850	6	4	404	24	27	035	18	24	096	9	−11
160	26	−26	405	17	−19	037	28	−30	099	9	8
260	11	6	407	23	−16	038	15	13	09,11	7	− 6
460	17	− 6	408	19	−16	03,11	16	19	09,15	4	1
560	21	−22	409	8	− 7	03,12	10	− 8	0,10,1	5	− 6
960	7	5	501	6	3	03,13	11	− 9	0,10,2	6	− 8
170	8	− 9	502	9	− 7	03,14	6	− 5	0,10,3	6	− 3
270	13	− 6	503	10	−12	03,18	4	− 5	0,10,5	7	− 6
470	21	23	504	31	−27	041	4	− 8	0,10,6	9	10
670	11	− 6	505	11	7	042	40	−37	0,10,8	11	− 6
870	7	9	507	9	9	043	18	−14	0,11,4	4	− 6
180	14	−22	509	15	−16	045	35	34	0,11,8	6	3
380	14	17	50,11	19	−18	046	9	9	0,12,3	4	5
480	10	−10	602	29	27	047	18	15	0,13,5	4	0
580	7	4	603	8	−12	048	16	− 7			
880	4	− 1	604	13	14	049	8	7			

[1] Value probably low owing to extinction. F = 123 used in Fourier synthesis.
[2] Intensity difficult to estimate because of spot shape.

It also follows that the constitution of β-caryophyllene alcohol (II), from which the chloride is derived, is in agreement with the chemical evidence, the tertiary hydroxyl group being replaced without inversion or rearrangement. Finally, from the arguments given by Barton, Bruun, and Lindsey (*loc. cit.*) it is clear that the present work supports the constitution (III) for caryophyllene. A further discussion of the stereochemistry of caryophyllene has recently been given by Aebi, Barton, and Lindsey (*J.*, **1953**, 3124), from whose paper formula (III) is taken.


(I)


(II)


(III)

Experimental

β-Caryophyllene Alcohol.—β-Caryophyllene, purified by fractional distillation, was hydrated by Asahina and Tsukamoto's method (*J. Pharm. Soc. Japan*, 1922, 463). β-Caryophyllene alcohol thus obtained was purified by steam-distillation and crystallisation from acetone, and had m. p. 92°.

β-Caryophyllene Chloride.—β-Caryophyllene alcohol (2·2 g.) and phosphorus pentachloride (2·1 g.) were allowed to react slowly. The product was isolated in the usual way, and after three crystallisations from ethyl alcohol had m. p. 62—63°.

β-Caryophyllene Bromide.—β-Caryophyllene alcohol (2·2 g.) and bromine (3·2 g.) with a minimum of acetic acid were boiled with a trace of iodine for 3 hr. Further bromine in acetic acid was then added and boiling continued for a further 3 hr. (Deussen, *J. pr. Chem.*, 1936, **145**, 31). The product was isolated and after five crystallisations from ethyl alcohol had m. p. 60—61°.

Crystal Data and Intensities.—Rotation, oscillation, and moving-film photographs were taken with copper $K\alpha$ radiation, $\lambda = 1{\cdot}542$ Å. The intensities were estimated visually by the multiple-film technique on moving-film photographs. In all, 232 bromide reflections and 254 chloride reflections were observed on the three principal axial zones, these representing 47% and 51% respectively of the 498 reflections possible for each crystal. The crystals of both substances are volatile and special precautions were necessary to preserve them for the time

Table 5. *Caryophyllene bromide. List of observed structure factors, with signs determined by replacement method.*

hkl	F	*hkl*	F	*hkl*	F	*hkl*	F	*hkl*	F	*hkl*	F
000	600 [1]	203	−65	607	−13	027	−90	048	−57	073	−50
200	70	205	−47	60,13	23	028	84	04,10	27	074	22
400	66	206	−74	701	−32	029	41	04,11	(±)12	075	67
020	81	208	−53	702	−36	02,10	−47	04,15	−21	077	−31
040	67	20,11	34	704	−33	02,13	−24	04,16	11	07,11	32
060	−44	20,13	37	70,12	23	02,14	30	051	−34	07,13	−24
080	(±)23	20,16	29	807	−12	02,16	−30	052	(+)16	081	45
002	−121	20,19	−12	903	−11	031	33	053	60	083	(±)11
004	(±)95	302	−85	904	−19	032	−105	054	(±)21	085	−41
006	121	305	−56	909	11	033	−104	055	−49	087	42
008	−81	306	−70	011	(−)15	034	121	056	35	089	−18
0010	39	307	−62	012	59	035	51	059	44	08,15	(−)13
0014	−35	309	−34	013	87	036	−29	05,11	−34	091	−32
		30,10	35	014	−131	037	−41	05,12	39	092	−25
103	41	30,12	29	015	(±)40	038	(±)14	05,13	18	093	38
104	−73	30,13	26	016	82	039	−14	05,14	−27	094	(±)13
105	−60	402	33	017	(±)29	03,10	32	061	−89	095	−25
107	−74	405	−57	01,10	−67	03,11	35	062	25	09,11	−16
109	−56	407	−38	01,12	47	03,12	−35	063	14	0,10,1	−28
10,10	21	408	−43	01,14	−30	03,13	(−)21	065	32	0,10,3	(+)13
10,11	−26	501	19	021	−85	041	30	067	−42	0,10,7	(−)13
10,12	21	502	−45	022	21	042	−81	068	32	0,10,8	(±)11
10,14	16	504	−81	023	36	043	−35	069	55	0,10,9	(+)11
10,17	28	509	−29	024	(±)52	045	24	06,11	(±)25	0,11,5	(+)11
201	−33	603	−38	025	76	046	45	06,15	(±)20		
202	125	605	−35	026	−56	047	50	072	−28		

[1] Calculated value.

required for the moving-film exposures. Of several methods tried, sealing in narrow lithium borate tubes was most successful, although this added to the background scatter. Crystals of approximately square cross section perpendicular to the rotation axis were employed to minimize absorption errors. The path length of the beam in the crystal, which was completely bathed in the radiation, varied from 0·2 to 0·35 mm. for different specimens of the bromide, and from 0·2 to 0·6 mm. for different specimens of the chloride. Some specimens were dipped in liquid air and rephotographed without noticeable change in intensities. It was concluded that extinction errors were not serious. Structure factors were derived by the usual mosaic crystal formula. The observed values are given in Tables 4 and 5.

Structure Calculations.—The various two-dimensional Fourier syntheses were calculated in the usual way, using the 3-figure strip and stencil method (Robertson, *J. Sci. Instr.*, **1948**, **25**, 28). The formulæ for the structure-factor calculations reduce to simple sine and cosine products when the origin is chosen on a two-fold axis, and this was done for all the projections. The signs of the calculated values of the structure factors given in Tables 4 and 5 are related to these non-coincident origins.

The theoretical scattering curves given by James and Brindley (*Phil. Mag.*, **1932**, **12**, 81) for chlorine and bromine were employed. The temperature factor was found to be abnormally high, and in the Debye–Waller factor B was given a value of $4{\cdot}4 \times 10^{-16}$. The carbon scattering curve finally used was that given by McWeeny (*Acta Cryst.*, **1951**, **4**, 513) for carbon (valence states) with $B = 3{\cdot}5 \times 10^{-16}$.

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CHEMISTRY DEPARTMENT, UNIVERSITY OF GLASGOW. [*Received, November 18th*, 1954.]

The Formulation of the Acidity Function J_0.

By V. GOLD.

[Reprint Order No. 5911.]

The exact relationship between the acidity functions H_0 and J_0 is defined. The applicability of several approximate relations for the calculation of J_0 is examined by reference to recent photometric data on ionisation of alcohols in sulphuric acid.

The difference between the calculated approximate J_0 functions and the experimental scale is thought to arise from the variation of acidity coefficient terms with the composition of the aqueous acid. On this basis, the dependence upon composition of certain combinations of activity coefficients in aqueous sulphuric acid has been determined.

Equations of General Validity.—It is the object of the acidity function J_0 (Gold and Hawes, *J.*, 1951, 2102) to provide a quantitative scale for the acidity of a medium towards secondary bases, *i.e.*, bases which ionise according to the general equations

$$ROH + HA \rightleftharpoons R^+ + A^- + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

or

$$ROH + 2HA \rightleftharpoons R^+ + 2A^- + H_3O^+ \quad . \quad . \quad . \quad . \quad . \quad (2)$$

This acidity depends on the composition of an acidic medium in a different manner from that which governs the ionisation of primary (or Brønsted) bases. A number of recent papers have dealt with applications of the J_0 function, and this interest has prompted the present re-examination of its formulation and the discussion of certain assumptions which were not considered in detail in the earlier paper.

The definition of the J_0 function is contained in equations (3), (4), and (5):

$$[R^+]/[ROH] = j_0 K_{ROH} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$J_0 = -\log_{10} j_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$J_0 = -pK_{ROH} + \log [ROH]/[R^+] \quad . \quad . \quad . \quad . \quad (5)$$

with the condition

$$J_0 \longrightarrow H_0 \text{ as } H_0 \longrightarrow pH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

K_{ROH} is a constant expressing the strength of the secondary base ROH. Equations (3)—(5) are analogous to the expressions defining the H_0 function

$$[BH^+]/[B] = h_0K_b^B \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$H_0 = -\log_{10}h_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$$H_0 = -pK_b^B + \log [B]/[BH^+] \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Equations (3)—(6) are regarded as the ultimate definition of J_0. Like the definition of H_0, it is based on the experimental measurement of ionisation ratios of indicators. Measurements of this type have been carried out by Murray and Williams (*J.*, 1950, 3323), Bevan and Williams (*Chem. and Ind.*, 1955, 171), Gold and Hawes (*loc. cit.*), and Deno, Jaruzelski, and Schriesheim (*J. Org. Chem.*, 1954, **19**, 155), but the published data do not as yet suffice for a calculation of the J_0 function over the whole composition range of an acid–water system.

Let us formally consider the ionisation of secondary bases in terms of the equilibrium

$$H^+ + ROH \rightleftharpoons H_2O + R^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

where the symbol H^+ denotes the proton in solution, as distinct from the hydroxonium ion H_3O^+. The equilibrium constant for (10) is given by

$$K = \frac{(H_2O)(R^+)}{(ROH)(H^+)} = \frac{[H_2O][R^+] \cdot f_{H_2O} \cdot f_{R^+}}{[ROH][H^+] \cdot f_{ROH} \cdot f_{H^+}} \quad . \quad . \quad . \quad . \quad . \quad (11)$$

[All equilibrium constants (K and $\boldsymbol{K}$) are defined in terms of activities, and activity coefficients (f) are referred to the standard state of an infinitely dilute aqueous solution.] Whenever necessary, we shall distinguish between concentrations (and activities) in molarity and mole-fraction units by affixing the subscripts C and N to the appropriately bracketed {[. .] or (. .)} chemical symbols. In (11), as in any other dimensionless ratio of concentrations or activities, the distinction is unnecessary. Activity coefficients are defined on a mole-fraction basis. Equation (11) may be rewritten as

$$K = \frac{[R^+]}{[ROH]} \cdot \frac{(H_2O)_N}{h_0}\left(\frac{f_B}{f_{BH^+}} \cdot \frac{f_{R^+}}{f_{ROH}}\right)\frac{55{\cdot}5}{\boldsymbol{K}_{H_3O^+}} \quad . \quad . \quad . \quad . \quad . \quad (12)$$

since

$$(H^+)_N = h_0 \cdot \frac{\boldsymbol{K}_{H_3O^+}}{55{\cdot}5} \cdot \frac{f_{BH^+}}{f_B} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

where f_B and f_{BH^+} are the activity coefficients relating to the acid–base pair BH^+,B used in the measurement of Hammett's acidity function H_0 over the particular range of solvent composition considered. $\boldsymbol{K}_{H_3O^+}$ is the acidity constant of the H_3O^+ ion, *i.e.*,

$$\boldsymbol{K}_{H_3O^+} = (H^+)_N(H_2O)/(H_3O^+) \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

(The constants $\boldsymbol{K}_{H_3O^+}$ and 55·5 appear in the above equation because, following Hammett's convention, $h_0 \longrightarrow [H_3O^+]_C$ at low concentrations of hydrogen ion.) Writing

$$K_{ROH} = K\boldsymbol{K}_{H_3O^+}/55{\cdot}5 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

and taking logarithms, we find that equation (12) becomes

$$-pK_{ROH} + \log \frac{[ROH]}{[R^+]} = H_0 + \log (H_2O)_N + \log \frac{f_B \cdot f_{R^+}}{f_{BH^+} \cdot f_{ROH}} \quad . \quad . \quad (16)$$

and, by comparison with equation (5),

$$J_0 = H_0 + \log (H_2O)_N + \log \frac{f_B \cdot f_{R^+}}{f_{BH^+} \cdot f_{ROH}} \quad . \quad . \quad . \quad . \quad . \quad (17)$$

It was shown by Hammett that ratios of the form f_B/f_{BH^+} were the same for several chemically different bases B. It *may* therefore be legitimate to equate

$$f_B/f_{BH^+} = f_{ROH}/f_{ROH_2^+} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

and hence derive

$$J_0 = H_0 + \log (H_2O)_N + \log f_{R^+}/f_{ROH_2^+} \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

From equation (14)

$$(H_2O)_N = K_{H_3O^+} \cdot (H_3O^+)_N/(H^+)_N \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (20)$$

and substitution of (20) in (11) leads to

$$K = K_{H_3O^+} (H_3O^+)_N(R^+)/(H^+)_N^2(ROH) \quad . \quad . \quad . \quad . \quad . \quad . \quad (21)$$

which, by substitution for $(H^+)_N$ from (13), becomes

$$K = \frac{[R^+]}{[ROH]} \cdot \frac{[H_3O^+]}{h_0^2} \left(\frac{f_B^2}{f_{BH^+}^2} \cdot \frac{f_{R^+}}{f_{ROH}} \cdot f_{H_2O^+} \right) \frac{55{\cdot}5^2}{K_{H_3O^+}} \quad . \quad . \quad . \quad . \quad (22)$$

This equation may be rewritten in the form

$$-pK_{ROH} + \log \frac{[ROH]}{[R^+]} = 2H_0 + \log [H_3O^+]_N + \log 55{\cdot}5 + \log \left(\frac{f_B^2}{f_{BH^+}^2} \cdot \frac{f_{R^+}}{f_{ROH}} \cdot f_{H_2O} \right) \quad . \quad . \quad (23)$$

and, therefore, from (5)

$$J_0 = 2H_0 + \log [H_3O^+]_N + \log \left(\frac{f_B^2}{f_{BH^+}^2} \cdot \frac{f_{R^+}}{f_{ROH}} \cdot f_{H_2O^+} \right) + 1{\cdot}74 \quad . \quad . \quad (24)$$

which, on the assumption contained in (18), becomes

$$J_0 = 2H_0 + \log [H_3O^+]_N + \log f_{ROH} \cdot f_{R^+} \cdot f_{H_2O^+}/f_{ROH_2^+}^2 + 1{\cdot}74 \quad . \quad . \quad (25)$$

Equations (17) and (24) are equally acceptable as rigorous thermodynamic formulations of J_0. They are not immediately useful for the purpose of predicting J_0 from the known properties of the solvent acid since both equations include terms involving unknown activity coefficients. It is therefore profitable to examine possible assumptions which eliminate the activity coefficients from the expression for J_0.

Approximate Expressions for J_0.—We shall examine in turn (i) the assumption that over the whole composition range considered

$$f_B \cdot f_{R^+}/f_{BH^+} \cdot f_{ROH} = 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (26)$$

which leads to an approximate expression for J_0:

$$J_0' = H_0 + \log (H_2O)_N \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (27)$$

[cf. Gold and Hawes, *loc. cit.*, equation (6)]; (ii) the assumption

$$(f_B^2 f_{R^+} f_{H_2O^+}/f_{BH^+}^2 f_{ROH}) = 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (28)$$

which leads to the alternative approximation to J_0:

$$J_0'' = 2H_0 + \log [H_3O^+]_N + 1{\cdot}74 \quad . \quad . \quad . \quad . \quad . \quad . \quad (29)$$

[cf. *idem, ibid.*, equations (9) and (10)]; and (iii) the assumption

$$f_B f_{R^+} f_{H_2O}/f_{BH^+} f_{ROH} = 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (30)$$

which leads to the approximation

$$J_0''' = H_0 + \log [H_2O]_N \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (31)$$

Not much is known in detail about the behaviour of activity coefficients in strong aqueous acids and we shall therefore test the adequacy of the alternative approximations by applying them to the experimental data on the ionisation of triarylmethanol indicators in

52—90% aqueous sulphuric acid obtained by Bevan and Williams (*loc. cit.*), who, over that composition range, established a *relative* scale of J_0 values ($J_0^{rel.}$) which is expected to differ from the time scale (*i.e.*, the scale anchored by the limiting condition $J_0 \longrightarrow H_0$ as $H_0 \longrightarrow$ pH) only by an additive term J_0^*, *i.e.*,

$$J_0 = J_0^{rel.} - J_0^* \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (32)$$

It must be pointed out that the $J_0^{rel.}$ scale is in part based on measurements with secondary bases carrying positive charges. Strictly speaking, therefore, their ionisation should be governed by the functions J_+, J_{++}, and J_{+++}. By analogy with the small difference between the H_0 and H_+ functions (Brand, Horning, and Thornley, *J.*, 1952, 1374), it would now seem that, for present purposes, this distinction may be neglected. Furthermore, the $J_0^{rel.}$ scale applies at a temperature of 20° whereas H_0, J_0', J_0'', and J_0''' refer to 25°. For the comparisons given in this paper this difference is probably unimportant (Bevan and Williams, personal communication).

The function J_0' was calculated and tabulated in the earlier paper (Gold and Hawes, *loc. cit.*), where it was merely designated by the symbol J_0. The functions J_0'' and J_0''' may be calculated if the concentrations of the various molecular species in aqueous acids are known. Such information is provided for sulphuric acid–water by the intensities of Raman spectra measured by Young ("Record of Chemical Progress," Spring Issue, 1951, p. 81, and personal communication; cf. Redlich, *Chem. Rev.*, 1949, **44**, 1). The accuracy with which $[H_3O^+]$ is known from these measurements is not very high but adequate for the approximate calculation of J_0''; the values of $[H_2O]$ are known with a precision sufficient for the calculation of J_0''' only up to ~80% sulphuric acid. An alternative procedure for obtaining $[H_3O^+]$ and $[H_2O]$ in the region of high concentrations of sulphuric acid would be their calculation in terms of an assumed equilibrium constant of the reaction $H_2O + H_2SO_4 \rightleftharpoons H_3O^+ + HSO_4^-$, as has been described in detail by Deno and Taft (*J. Amer. Chem. Soc.*, 1954, **76**, 244). However, at present the use of values derived from Raman spectra seems to be less open to objection and has been adopted in this work, but most of the conclusions remain unaffected if the alternative procedure is followed. At low acid concentrations all three approximation functions approach each other and go over into H_0.

A test of the functions is illustrated by Fig. 1, where H_0, J_0', J_0'', and J_0''' are plotted against $J_0^{rel.}$. It is seen that the J_0 approximations all agree with the experimental data very much better than H_0. J_0'' is more satisfactory than J_0' which, in turn, is superior to the approximation J_0'''. These results are thought to express the adequacy of the assumptions contained in equations (26), (28), and (30).

Behaviour of Activity Coefficients in the System Sulphuric Acid–Water.—The combination of the experimental $J_0^{rel.}$ values with the functions J_0', J_0'', and J_0''' permits some conclusions concerning the dependence of certain combinations of activity coefficients upon solvent composition in the range 52—90% sulphuric acid. From (17), (27), and (32)

$$J_0^{rel.} - J_0' = \log f_B f_{R^+} / f_{BH^+} f_{ROH} + J_0^* \quad . \quad . \quad . \quad . \quad . \quad (33)$$

from (24), (29), and (32)

$$J_0^{rel.} - J_0'' = \log f_B^2 f_{R^+} f_{H_3O^+} / f_{BH^+}^2 f_{ROH} + J_0^* \quad . \quad . \quad . \quad . \quad (34)$$

and from (17), (31), and (32),

$$J_0^{rel.} - J_0''' = \log f_B f_{R^+} f_{H_2O} / f_{BH^+} f_{ROH} + J_0^* \quad . \quad . \quad . \quad . \quad (35)$$

provided that the ratios f_{R^+}/f_{ROH} and f_B/f_{BH^+} may both be assumed to be independent of the nature of the bases employed in indicator studies over the range concerned. Furthermore, combination of the calculated functions J_0', J_0'', and J_0''' gives certain other combinations of activity coefficients over the composition range 0—90% sulphuric acid:

$$J_0'' - J_0' = \log f_B f_{H_3O^+} / f_{BH^+} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (36)$$

$$J_0''' - J_0' = \log f_{H_2O} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (37)$$

and

$$J_0''' - J_0'' = \log f_B f_{H_2O} / f_{BH^+} f_{H_3O^+} \quad . \quad . \quad . \quad . \quad . \quad . \quad (38)$$

Of course, the calculation of the activity coefficient ratios contained in equations (36)—(38) does not require the concept of the J_0 functions but can be thought to follow from the experimental values of concentrations of molecular species in the system. Deno and Taft (*loc. cit.*) carried out a calculation of $\log f_{H_2O}$ in this manner.

FIG. 1.

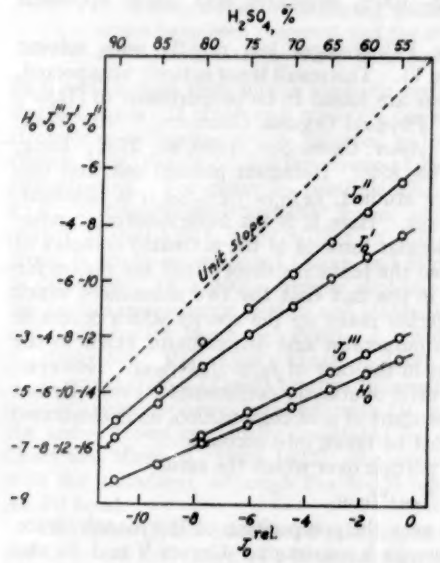


FIG. 3.

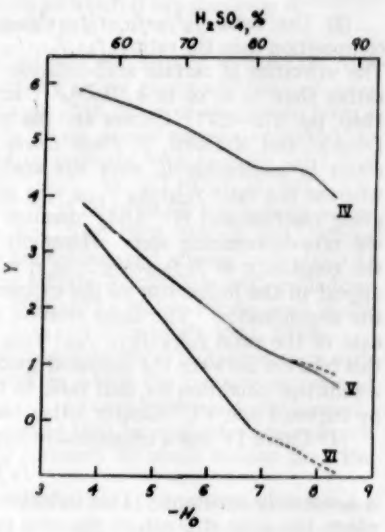
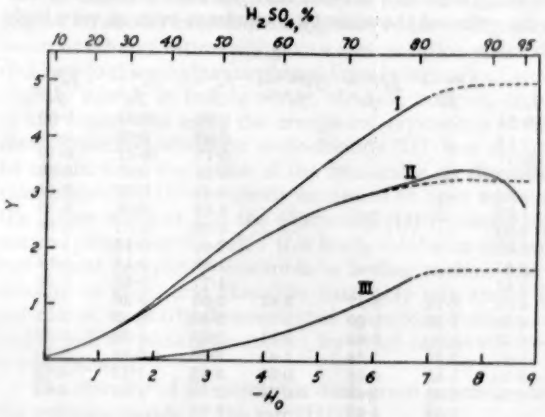


FIG. 2.



I; $Y = \log (f_{BH^+} f_{H_2O} / f_B f_{H_3O^+})$.
II; $Y = \log (f_{BH^+} / f_B f_{H_3O^+})$.
III; $Y = \log f_{H_2O}$.
IV; $Y = \log (f_B^3 f_{B^+} f_{H_3O^+} / f_{BH^+}^3 f_{ROH}) + J_0^*$.
V; $Y = \log (f_B f_{B^+} / f_{BH^+} f_{ROH}) + J_0^*$.
VI; $Y = \log (f_B f_{B^+} f_{H_2O} / f_{BH^+} f_{ROH}) + J_0^*$.

Equations (33)—(38) express the deviations of the approximate J_0 function from each other and from the experimental values, and the calculated terms are now more sensitive to the exact choice of the values of $(H_2O)_N$, $[H_3O^+]_N$, and $[H_2O]_N$. The curves given by us are again based on Young's data (*loc. cit.*) and values of $(H_2O)_N$ selected by Gold and Hawes, but we have indicated where the adoption of Deno and Taft's suggestions would lead to a qualitatively different result (broken lines in Figs. 2 and 3). The behaviour of some

combinations of activity coefficients in sulphuric acid–water is shown in Figs. 2 and 3. The following features of the curves are noteworthy.

(1) The activity coefficient of water (curve III) remains virtually constant at unity up to a concentration of 30% sulphuric acid and thereafter its variation is slower than that of any other combination of activity coefficients examined.

(2) Curves IV and V do not support Deno and Taft's tentative suggestion that activity coefficients for any species in the region 83—100% sulphuric acid might approach constancy.

(3) The ratio $f_B^2 f_{B^+} f_{H_2O^+} / f_{BH^+}^2 f_{ROH}$ (curve IV) changes less rapidly with solvent composition than the ratio $f_B f_{B^+} / f_{BH^+} f_{ROH}$ (curve V). This result is not entirely unexpected. The velocities of certain acid-catalysed reactions are found to be proportional to $[H_3O^+]$ rather than to h_0 or to $h_0(H_2O)_N$ (Hammett, "Physical Organic Chemistry," New York, 1940, pp. 273—277; Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2791; Long, Dunkle, and McDevit, *J. Phys. Chem.*, 1951, **55**, 829). Hammett pointed out that this result is intelligible if, over the acidity range studied, $f_K f_{H_2O^+} / f_{(K \cdots OH_2^+)}$ is constant, whereas the ratio $f_{KH^+} / f_{(K \cdots OH_2^+)}$ is not constant. Here K is the basic substrate undergoing reaction and $K \cdots OH_2^+$ denotes the molecular formula of the activated complex of the rate-determining step. Hammett advanced the tentative theory that the reason for the constancy of $f_K f_{H_2O^+} / f_{(K \cdots OH_2^+)}$ might lie in the fact that the two substances which appear in the numerator of the expression together make up the species which occurs in the denominator. The same relation between numerator and denominator exists in the case of the ratio $f_B^2 f_{B^+} f_{H_2O^+} / f_{BH^+}^2 f_{ROH}$ but not in the case of $f_B f_{B^+} / f_{BH^+} f_{ROH}$. However, this relation between the chemical species in a ratio of activity coefficients is evidently not a sufficient condition for that ratio to be independent of acid composition, as is illustrated by curves I and VI. Clearly, other factors must be taken into account.

(4) Curve IV has a considerable horizontal portion over which the ratio

$$f_B^2 f_{B^+} f_{H_2O^+} / f_{BH^+}^2 f_{ROH}$$

is accurately constant. This inflexion occurs near the composition of the monohydrate, where the ionic strength of the acid passes through a maximum. Curves V and VI also appear to be less steep in this region than at lower acidity. It may therefore be profitable to analyse activity coefficients in sulphuric acid on the basis that the ionic strength of the solution is a specific factor affecting the value of the activity coefficients even at very high concentrations of ions.

H_2SO_4, %	$J_0^{rel.}$ [1]	J_0' [2]	J_0''	J_0'''	$J_0^{rel.} - J_0'$	$J_0^{rel.} - J_0''$	$J_0^{rel.} - J_0'''$	$J_0' - J_0''$	$J_0'' - J_0'$	$J_0''' - J_0''$
5	—	+0·23	+0·24	+0·24	—	—	—	0·01	0·01	0·00
10	—	−0·18	−0·27	−0·18	—	—	—	0·09	0·00	0·09
15	—	−0·58	−0·76	−0·57	—	—	—	0·18	0·01	0·19
20	—	−0·95	−1·26	−0·93	—	—	—	0·31	0·02	0·33
25	—	−1·30	−1·79	−1·28	—	—	—	0·49	0·02	0·51
30	—	−1·66	−2·35	−1·62	—	—	—	0·69	0·04	0·73
35	—	−2·07	−2·96	−2·00	—	—	—	0·89	0·07	0·96
40	—	−2·52	−3·68	−2·41	—	—	—	1·16	0·11	1·27
45	—	−3·05	−4·51	−2·87	—	—	—	1·46	0·18	1·64
50	—	−3·67	−5·44	−3·41	—	—	—	1·77	0·26	2·03
55	−0·59	−4·37	−6·46	−4·01	3·78	5·87	3·42	2·09	0·36	2·45
60	−1·81	−5·11	−7·50	−4·59	3·30	5·69	2·78	2·39	0·52	2·91
65	−3·12	−5·92	−8·60	−5·23	2·80	5·48	2·11	2·68	0·69	3·37
70	−4·52	−6·91	−9·76	−5·97	2·39	5·24	1·45	2·85	0·94	3·79
75	−6·10	−7·93	−10·98	−6·70	1·83	4·88	0·60	3·05	1·23	4·28
80	−7·75	−9·10	−12·24	−7·55	1·35	4·49	−0·20	3·14	1·55	4·69
85	−9·37	−10·41	−13·90	—	1·04	4·53	—	3·49	—	—
90	−10·92	−11·66	−15·04	—	0·74	4·12	—	3·38	—	—
95	—	−13·37	−16·22	—	—	—	—	2·85	—	—

[1] From Bevan and Williams (*loc. cit.*). [2] From Gold and Hawes (*loc. cit.*).

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The Constitution of Complex Metallic Salts. Part XV. Palladium Derivatives of o-Dimethylaminophenyldimethylarsine.*

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A number of co-ordinated palladium derivatives of the above amine-arsine have been prepared, and the conditions under which it can thus form a chelate ring with the metal have been investigated.

It is well known that simple aliphatic tertiary amines will not usually co-ordinate with metallic salts. If however a molecule contains a tertiary amine group and another more strongly co-ordinating group, situated so that the two groups could co-operate to form a chelate ring, the co-ordinating power of the tertiary amine group may be considerably strengthened. For example, triethylamine does not co-ordinate with metallic salts, but 2 : 2′ : 2″-triaminotriethylamine forms stable salts such as $[Cl_2PtN(C_2H_4\cdot NH_2)_3]Cl_2$, $[NiN(C_2H_4\cdot NH_2)_3]SO_4$, and $[(SCN)_2CoN(C_2H_4\cdot NH_2)_3]SCN$, in all of which the tertiary amine group is firmly co-ordinated (Mann and Pope, *Proc. Roy. Soc.*, 1925, **109**, *A*, 446; Mann, *J.*, 1926, 482; 1929, 409). Simple aliphatic tertiary phosphines and arsines, in contrast to the amines, co-ordinate readily and stably with many metals, particularly with palladium and platinum (cf. Mann and Purdie, *J.*, 1935, 1549; 1936, 873; Mann, Purdie, and Wells, *J.*, 1936, 1503; 1937, 1828; Chatt, *J.*, 1950, 2301; Chatt and Wilkins, *J.*, 1951, 2532).

It was therefore of great interest to investigate the co-ordination of palladium salts with *o*-dimethylaminophenyldimethylarsine (I), a compound in which the tertiary amine and the arsine group are ideally orientated for chelation [cf. *o*-phenylenebis(dimethylarsine); Chatt and Mann, *J.*, 1939, 1622]; the amine group might thus be enabled to co-ordinate with the palladium, although the N–Pd bond would certainly be much weaker than the As–Pd bond.

The arsine (I) is a colourless liquid prepared by the interaction of dimethyliodoarsine and the Grignard derivative of *o*-bromodimethylaniline: it readily forms a monomethiodide, in which undoubtedly the arsine group has become quaternised.

The arsine (I) in ethanolic solution reacted with hot aqueous potassium palladochloride to give an almost insoluble dark green product; digestion of this product with much boiling water or ethanol ultimately gave a clear solution which deposited the pale yellow crystalline dichloro-(*o*-dimethylaminophenyldimethylarsine)palladium (II). This compound is only slightly soluble in boiling water, ethanol, acetone, or benzene. When however an excess of the arsine was used, the orange-red crystalline monochlorobis(*o*-dimethylaminophenyldimethylarsine)palladium monochloride (III) was obtained. This monochloride could also be obtained by the action of the free arsine on the compound (II): conversely, when the monochloride (III) was slowly heated in an open vessel almost to its normal m. p., some of the arsine was lost and the compound (II) regenerated. The monochloride (III) has the normal properties of a salt: it is freely soluble in cold water, moderately so in cold ethanol, but almost completely insoluble in boiling acetone and benzene. The fact that only one chlorine is ionic, and therefore that only one amine-arsine molecule is chelated to the palladium, is clearly demonstrated by mixing cold aqueous solutions of the chloride (III) and of sodium picrate (in excess), by which means the crystalline monopicrate (IV; X = Cl) is precipitated.

The identity of the insoluble dark green product was not investigated: it may well be the palladochloride of the salt (III).

Similarly the arsine (I) when treated with potassium palladobromide gave a brown insoluble product which on digestion with boiling ethanol furnished the yellowish-orange crystalline dibromo-(*o*-dimethylaminophenyldimethylarsine)palladium (V) which is insoluble in boiling water and only very sparingly soluble in the common hot organic solvents, including dioxan. Treatment of either this compound or potassium palladobromide with the appropriate amount of the free arsine (I) produced deep ruby-red crystals

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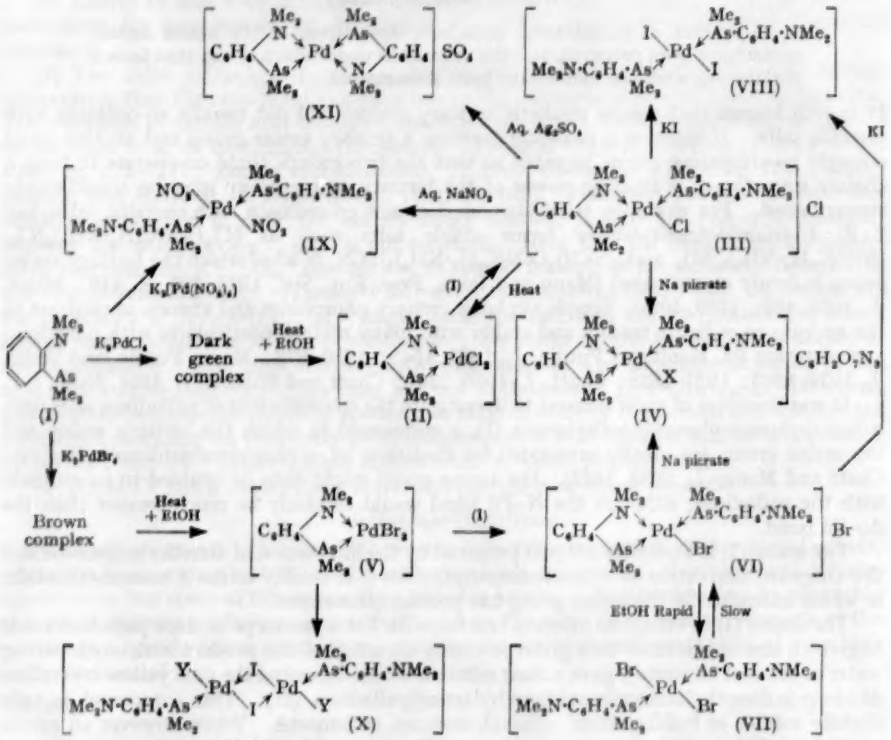
of monobromobis-(*o*-dimethylaminophenyldimethylarsine)palladium monobromide (VI), m. p. 170—172°. This salt is readily soluble in warm water (from which it can be recrystallised unchanged), moderately so in hot ethanol, slightly soluble in boiling acetone, and perceptibly more so in boiling benzene. Its constitution was also shown by its conversion into the crystalline monopicrate (IV; X = Br).



The monobromide (VI) was isolated by slow recrystallisation from ethanolic solution. When, however, recrystallisation from ethanol was performed as rapidly as possible, or when a suspension in benzene was boiled until clear, then concentrated and cooled, the non-ionic isomeric dibromobis-(*o*-dimethylaminophenyldimethylarsine)palladium (VII) was obtained as orange-yellow crystals, also of m. p. 170—172°. This isomer has the properties of a true covalent compound: it dissolves readily in cold benzene, is much more soluble in ethanol than the monobromide (VI), and only very slowly dissolves in boiling water, with conversion into the monobromide (VI). The interconversion of the two compounds is a ready process: the isomer (VII) always recrystallises unchanged from benzene, but slow recrystallisation from ethanol (in which the two isomers must exist in equilibrium) furnishes the monobromide (VI). Moreover, their identical m. p.s indicate a complete thermal conversion into one form which proves to be the isomer (VII). The equilibrium which exists in ethanolic solution between the compounds (VI) and (VII) represents a very rare type of tautomerism.

Aqueous or aqueous-ethanolic solution of the monochloride (III) or the monobromide (VI) when treated with potassium iodide deposited the orange-red di-iodobis-(*o*-dimethylaminophenyldimethylarsine)palladium (VIII). This compound shows no ionic properties: it is insoluble in boiling water, moderately soluble in ethanol and readily soluble in cold acetone and benzene, and in the last solvent shows a normal molecular weight.

The chloro-, bromo-, and iodo-compounds in this diarsine series thus show a noteworthy transition, since in the chloro-series apparently only the salt (III) can be obtained, whereas in the bromo-series the salt (VI) and the covalent isomer (VII) can be isolated, and in the iodo-series only the covalent form (VIII) is obtained. The absence of an iodo-derivative having the chelated arsine ring system is striking.

Treatment of an aqueous solution of potassium palladonitrite, $K_2[Pd(NO_2)_4]$, with the arsine (I), or of a similar solution of the monochloride (III) with sodium nitrite, produced dinitritobis-(*o*-dimethylaminophenyldimethylarsine)palladium (IX), as very pale yellow (almost colourless) crystals. The covalent structure (IX) is shown by the solubilities of this compound in water, ethanol, acetone, and benzene, which are closely similar to those of the di-iodo-compound (VIII): moreover, the compound (IX) also shows a normal molecular weight in benzene. The chelated ring in the monochloride (III) must therefore be broken at the N–Pd link during the above reaction, as in the similar preparation of the derivative (VIII). The fact that a fundamental change in structure has thus occurred is shown by mixing cold moderately concentrated aqueous solutions of (III) and of sodium nitrite: the mixture remains clear for some time before the insoluble dinitrito-compound (IX) begins to separate; and even if more concentrated cold solutions are employed, only a faint turbidity initially appears, although separation of (IX) is now less delayed.

When an ethanolic solution of the compound (IX) was treated with an excess of sodium iodide in acetone, heavy well-formed crystals of the di-iodo-derivative (VIII) slowly separated.

The dibromo-compound (V) is converted, when its suspension in aqueous potassium iodide is boiled for several hours, into a deep orange compound of empirical formula $C_{10}H_{16}NBrIAsPd$: the similar use of an acetone solution of sodium iodide gives a deep red product of composition $C_{10}H_{16}NI_2AsPd$. There is insufficient evidence to determine the structure of these compounds. They may be the simple chelated bromo-iodo- and di-iodo-compounds corresponding to (II) and (V), but it is more probable that they are the bridged compounds dibromobis-(*o*-dimethylaminophenyldimethylarsine)-$\mu\mu'$-di-iododipalladium (X; Y = Br) and the di-iodo-$\mu\mu'$-di-iodo-analogue (X; Y = I), respectively, for the following reasons. (*a*) The potassium iodide, employed in excess in the above preparation, would be unlikely to form a mixed bromo-iodo-compound of type (V) but, since the stability of halogen atoms in the bridged condition is known to increase in the order Cl < Br < I, the formation of the compound (X; Y = Br) is not unexpected. This reaction would have some analogies to that shown by dichlorobistri-*n*-butylphosphine-$\mu\mu'$-dichlorodipalladium when heated in an aqueous-ethanolic suspension with an excess of potassium oxalate; the bridged chlorine atoms are replaced by a bridged oxalate radical, but the unbridged chlorine atoms are unaffected (Mann and Purdie, *loc. cit.*). (*b*) The compounds (II) and (V) blacken and decompose without melting, whereas the above red iodo-compound melts to a clear red liquid which only slowly decomposes. (*c*) The formation of the compound (VIII) indicates that the co-ordinating power of the iodine atom disrupts the N–Pd link, a process which in this series must lead to the bridged derivatives. The high molecular weights and low solubilities of the two compounds precluded decisive molecular-weight determinations.

The reason why the above halogeno- and nitrito-compounds contain no derivative having two molecules of the arsine chelated to one atom of palladium is apparently that the co-ordinating power of chlorine and bromine is sufficiently strong to break one of the two rings [cf. (III) and (VI)], whilst that of iodine and the nitro-group suffices to break both [cf. (VIII) and (IX)]. An anion of very weak co-ordinating power, which therefore would not enter the metallic complex, should allow the two chelate rings to exist. This we find to be the case. The chloride (III), when treated in aqueous solution with an equivalent of silver sulphate, gave the hydrated crystalline bis-(*o*-dimethylaminophenyldimethylarsine)palladium sulphate (XI): the fact that the water molecules had not co-ordinated with the palladium with rupture of the N–Pd link was shown by the conversion of the sulphate into the crystalline anhydrous dipicrate (as XI).

The co-ordinated derivatives of dialkyl-*o*-dimethylaminophenylphosphines and of dialkyl-(*o*-dialkylphosphinophenyl)arsines with various metals will be described later.

Experimental

Molecular weights were determined ebullioscopically.

o-Dimethylaminophenyldimethylarsine (I).—A solution of *o*-bromodimethylaniline (10·6 g.) in ether (45 c.c.) was slowly added to magnesium (1·6 g.) under ether (5 c.c.) in a nitrogen atmosphere. The resulting Grignard solution was boiled under reflux for 30 min., and then cooled in ice-water with stirring whilst a solution of dimethyliodoarsine (12·5 g., 1·02 mols.) in ether (30 c.c.) was added dropwise. A heavy dark oil separated, but slowly dissolved when the mixture was boiled for 2 hr.: the product was then cooled as before and hydrolysed with aqueous ammonium chloride. The dried ethereal layer on distillation gave the *arsine* (I), a colourless mobile refractive liquid (7·9 g., 68%), b. p. 110—114°/11 mm., having an unpleasant odour (Found: N, 6·1. $C_{10}H_{16}NAs$ requires N, 6·2%).

The arsine in ethereal solution readily gave a colourless *monomethiodide*, m. p. 221—222° (from methanol–ether) (Found: C, 36·0; H, 4·9; N, 4·1. $C_{11}H_{19}NIAs$ requires C, 35·9; H, 5·1; N, 3·8%): this salt gave a yellow *monomethopicrate*, m. p. 179—181° (from ethanol) (Found: C, 43·7; H, 4·3; N, 12·4. $C_{17}H_{21}O_7N_4As$ requires C, 43·5; H, 4·2; N, 12·0%).

Chloro-derivatives.—(*a*) Hot concentrated aqueous potassium palladochloride was treated with just sufficient of the arsine (I) in ethanol to discharge its colour. The precipitated dark green product was collected and boiled with a large volume of water until a clear solution was obtained: the crystals which separated on cooling were recrystallised from much ethanol, and afforded *dichloro-(o-dimethylaminophenyldimethylarsine)palladium* (II), glistening pale yellow plates, which darkened and became black at 215—220° but gave no effervescence below 320° (Found: C, 29·8; H, 3·9%; *M*, in ethylene dichloride, 380. $C_{10}H_{16}NCl_2AsPd$ requires C, 29·8; H, 3·9%; *M*, 402·7).

(*b*) Solutions of potassium palladochloride (0·5 g.) in water (5 c.c.) and of the arsine (I) (0·7 g., 2 mols.) in ethanol (5 c.c.) were mixed and boiled until a clear solution was obtained, 50% aqueous ethanol being added when necessary. The solution was evaporated to dryness and the residue extracted with boiling absolute ethanol. The filtered extract, when diluted with ether and vigorously scratched, deposited *monochlorobis-(o-dimethylaminophenyldimethylarsine)-palladium monochloride* (III), which, when carefully recrystallised from ethanol by the addition of ether, formed beautiful orange-red prisms, m. p. 187—188° (decomp.) (Found: C, 38·3; H, 5·1; N, 4·5. $C_{20}H_{32}N_2Cl_2As_2Pd$ requires C, 38·2; H, 5·1; N, 4·4%). Mixing cold aqueous solutions of this salt and of sodium picrate precipitated the *monopicrate* (IV; X = Cl), yellow needles, m. p. 171—172°, from ethanol (Found: C, 38·2; H, 4·0; N, 8·6. $C_{26}H_{34}O_7N_5ClAs_2Pd$ requires C, 38·0; H, 4·1; N, 8·5%): the presence of chlorine in this salt was confirmed.

When a finely powdered sample of the monochloride (III) was slowly heated to *ca.* 160°, it became pale yellow as amine-arsine was lost with conversion into the compound (II), which then could be readily recrystallised from ethanol. When a hot ethanolic solution of the compound (II) was treated with the arsine (1 mol.), the solution immediately became deep orange and, when considerably concentrated, cooled, and diluted with ether, deposited the pure monochloride (III), m. p. 186—187° (decomp.), alone and mixed.

Bromo-derivatives.—(*a*) The addition of an ethanolic solution of the arsine (I) to a hot concentrated aqueous solution of potassium palladobromide until the colour of the latter had faded precipitated a dark khaki-coloured product, which, when collected and digested with much boiling ethanol, ultimately gave an almost clear solution. The filtered cooled solution deposited *dibromo-(o-dimethylaminophenyldimethylarsine)palladium* (V), yellowish-orange needles, which began to blacken at *ca.* 220° and effervesced at 240° (Found: C, 24·7; H, 3·5; N, 3·1%; *M*, in ethylene dibromide, 470. $C_{10}H_{16}NBr_2AsPd$ requires C, 24·4; H, 3·2; N, 2·8%; *M*, 491·7).

(*b*) An ethanolic solution of the arsine (I) was added to a vigorously stirred hot concentrated solution of potassium palladobromide until a clear yellow solution containing a slight excess of (I) was obtained. The solution, diluted with a small amount of water and cooled, deposited *monobromobis-(o-dimethylaminophenyldimethylarsine)palladium monobromide* (VI), which on slow crystallisation from ethanol formed ruby-red prisms, m. p. 170—172° (decomp.) (Found: C, 33·5; H, 4·5; N, 4·2. $C_{20}H_{32}N_2Br_2As_2Pd$ requires C, 33·5; H, 4·4; N, 3·9%). This salt crystallised unchanged when its warm aqueous solution was cooled. This aqueous solution, when added to aqueous sodium picrate, precipitated the *monopicrate* (IV; X = Br), yellow crystals (from ethanol), m. p. 174—175° (Found: C, 36·3; H, 4·0; N, 8·2. $C_{26}H_{34}O_7N_5BrAs_2Pd$ requires C, 36·1; H, 3·9; N, 8·1%); the presence of bromine was confirmed.

A hot concentrated ethanolic solution of the monobromide (VI), when rapidly cooled with

vigorous stirring and scratching, deposited *dibromobis-(o-dimethylaminophenyldimethylarsine)-palladium* (VII), orange-yellow tablets, m. p. 170—172° (decomp.) (Found: C, 33·8; H, 4·5; N, 4·0. $C_{20}H_{32}N_2Br_2As_2Pd$ requires C, 33·5; H, 4·4; N, 3·9%). A suspension of the monobromide (VI) in benzene when boiled slowly dissolved and the clear solution on cooling deposited the isomer (VII). The monobromide (VI), when heated just above its m. p. and then cooled, was converted into the isomer (VII) without change of m. p.: this conversion was shown in particular by the ready solubility of the product in cold benzene, in which the monobromide (VI) is very slightly soluble.

Iodo-derivative.—An excess of aqueous potassium iodide, when added to a cold aqueous solution of the monochloride (III), precipitated *di-iodobis-(o-dimethylaminophenyldimethylarsine)-palladium* (VIII), deep orange-red crystals, m. p. 206—207° (decomp.) from ethanol (Found: C, 29·4; H, 4·1%; *M* in benzene, 780. $C_{20}H_{32}N_2I_2As_2Pd$ requires C, 29·6; H, 3·9%; *M*, 810·5). The same compound was obtained when the monobromide (VI) in aqueous-ethanol solution was used.

Nitrito-derivative.—A warm stirred concentrated aqueous solution of potassium palladonitrite, when treated with a slight excess of the arsine (I) in ethanol, readily deposited *dinitritobis-(o-dimethylaminophenyldimethylarsine)palladium* (IX), very faint greenish-yellow (almost colourless) crystals, m. p. 180° (decomp.), from ethanol (Found: C, 37·2; H, 5·3; N, 8·5%; *M* in benzene, 640. $C_{20}H_{32}O_4N_4As_2Pd$ requires C, 37·0; H, 4·9; N, 8·6%; *M*, 648·8). A cold aqueous solution of the monochloride (III), when mixed with an excess of sodium nitrite solution, remained initially clear and then slowly deposited the compound (IX) which, after crystallisation from ethanol, had m. p. 179—180° (decomp.), unchanged on admixture with the above sample.

An ethanolic solution of the compound (IX), when diluted with a small excess of a saturated acetone solution of sodium iodide, slowly deposited crystals of the di-iodo-compound (VIII), m. p. 206° (decomp.), unchanged by admixture with the above authentic compound.

Bridged Compounds.—(*a*) The finely powdered dibromo-compound (V), when digested for several hours with boiling aqueous potassium iodide, was converted into *dibromobis-(o-dimethylaminophenyldimethylarsine)-μμ′-di-iododipalladium* (X; Y = Br), deep orange crystals, m. p. 229—230° (decomp.), from ethanol (Found: C, 22·0; H, 2·9; N, 2·9. $C_{20}H_{32}N_2Br_2I_2As_2Pd_2$ requires C, 22·2; H, 2·9; N, 2·6%).

(*b*) When the compound (V) was similarly digested for 4 hr. with an excess of sodium iodide in acetone, a marked change in colour occurred, and the solution, when concentrated and diluted with water, deposited the *di-iodo-μμ′-di-iodo*-analogue (X; Y = I), deep red crystals, m. p. 221—222° (slow decomp.), from ethanol (Found: C, 20·6; H, 2·7; N, 2·3. $C_{20}H_{32}N_2I_4As_2Pd$ requires C, 20·5; H, 2·7; N, 2·3%).

The Sulphate (XI).—Warm aqueous solutions of the chloride (III) (34 mg.) and silver sulphate (17 mg., 1 mol.) were mixed, vigorously shaken, and filtered. The filtrate, evaporated in a desiccator at room temperature, deposited hydrated clear pale yellow plates, which were very soluble in water, methanol, ethanol, and acetone, but insoluble in boiling benzene. When confined in a vaccum over phosphoric anhydride, they rapidly underwent partial dehydration to *bis-(o-dimethylaminophenyldimethylarsine)palladium sulphate trihydrate* (XI), a fine very pale buff coloured powder, m. p. 178—180° (decomp.) (Found: C, 33·8; H, 5·5. $C_{20}H_{32}O_4N_2SAs_2Pd,3H_2O$ requires C, 33·9; H, 5·4%). The addition of this sulphate to sodium picrate, both in cold aqueous solution, precipitated the *dipicrate* (as XI), a dark yellow microcrystalline powder, m. p. 188—190° (decomp.), after crystallisation from water containing a small proportion of ethanol (Found: C, 37·75; H, 3·9; N, 11·1. $C_{32}H_{36}O_{14}N_8As_2Pd$ requires C, 37·9; H, 3·6; N, 11·1%).

Great accuracy is not claimed for the determination of the molecular weights of the compounds (II) and (V), owing to their very low solubility in boiling solvents: the values obtained however leave no doubt concerning the order of the molecular weights.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 11th*, 1954.]

Orientation Effects in the Diphenyl Series. Part XIV. The Thermal Decomposition of Some "Diazoperbromides."*

By Shiu May Loh and E. E. Turner.

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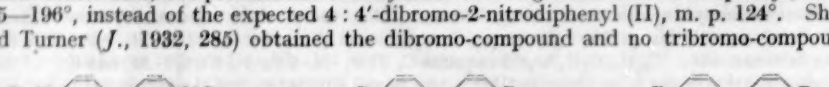
The bisdiazonium perbromide derived from 2-nitrobenzidine decomposes in hot glacial acetic acid to give 2′ : 4 : 4′-tribromo- and 4 : 4′-dibromo-2-nitrodiphenyl. The tribromo-compound appears to be formed by an intramolecular mechanism.

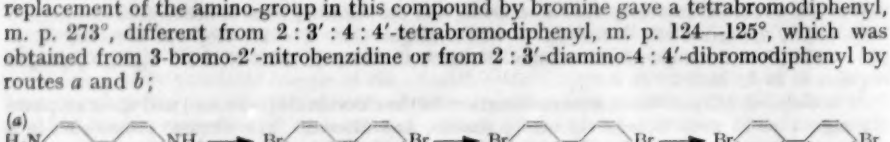
It was observed by Le Fèvre and Turner (*J.*, 1926, 2041) that the bisdiazonium perbromide (I) derived from 2-nitrobenzidine behaved abnormally when allowed to decompose in hot glacial acetic acid, the product most easily isolated being a tribromonitrodiphenyl, m. p. 195—196°, instead of the expected 4 : 4′-dibromo-2-nitrodiphenyl (II), m. p. 124°. Shaw and Turner (*J.*, 1932, 285) obtained the dibromo-compound and no tribromo-compound



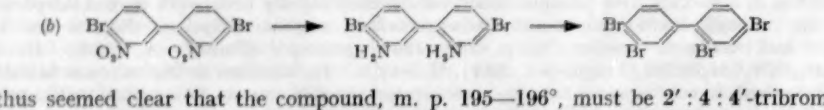
(I) (II) (III)

by carrying out the decomposition in boiling ethanol (cf. Saunders, *Amer. Chem. J.*, 1891, **13**, 496). The tribromo-compound was regarded by Le Fèvre and Turner as being 3′ : 4 : 4′-tribromo-2-nitrodiphenyl (III) since (*a*) it seemed inconceivable that the third bromine atom had entered the nucleus bearing the nitro-group and (*b*) by analogy with the nitration of 4 : 4′-dibromo-2-nitrodiphenyl, 3′-substitution seemed to be more probable than 2′-substitution. The most interesting thing, of course, was the entry of the third bromine atom into what would be regarded as a non-reactive system.

Reduction of the tribromo-compound gave a tribromo-aminodiphenyl, m. p. 154°, and replacement of the amino-group in this compound by bromine gave a tetrabromodiphenyl, m. p. 273°, different from 2 : 3′ : 4 : 4′-tetrabromodiphenyl, m. p. 124—125°, which was obtained from 3-bromo-2′-nitrobenzidine or from 2 : 3′-diamino-4 : 4′-dibromodiphenyl by routes *a* and *b*;



It thus seemed clear that the compound, m. p. 195—196°, must be 2′ : 4 : 4′-tribromo-2-nitrodiphenyl (IV). This has been proved by performing the operations shown below :



The product was identical with the compound of m. p. 195—196° and was convertible in two stages into 2 : 2′ : 4 : 4′-tetrabromodiphenyl, m. p. 273°. The latter was also obtained by carrying out a benzidine rearrangement on 2 : 2′-dibromohydrazobenzene, followed by a diazonium perbromide replacement. It could not, however, be isolated from the mixture obtained by heating 2 : 4-dibromoiodobenzene with copper powder.

The decomposition of the bisdiazonium perbromide derived from 2-nitrobenzidine proceeds with some tar formation in boiling glacial acetic acid but has now been found to

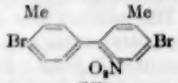
* Part XIII, *J.*, 1937, 266.

give an easily worked product when the decomposition in acetic acid is carried out at 95°. This has enabled us to make a more complete study of the decomposition, which under these conditions gives the tribromonitro-compound together with about twice its weight of 4 : 4′-dibromo-2-nitrodiphenyl. This is of some importance, as it supports the suggestion that the dibromo-compound, as such, is not the precursor of the tribromo-compound. This suggestion became more acceptable when we found that decomposition of the bisdiazonium perbromide in acetic acid in presence of one molecular proportion of the dibromo-compound gave the same yield of tribromo-compound as was obtained in absence of the dibromo-compound. Incidentally, we had already tried but failed to effect the bromination of the dibromonitro-compound by the action of bromine in boiling acetic acid solution.

It seems reasonable to conclude that in the decomposition of the bisdiazonium perbromide derived from 2-nitrobenzidine the diazonium group attached to the ring containing the nitro-group is (perhaps unexpectedly) less stable than the other diazonium group, so that bromination leading to the tribromonitro-compound occurs while the ring not containing the nitro-group retains the (*meta*-directing) diazonium grouping. Only in this way can one account for the 2′-bromination. The hitherto unknown 2 : 4 : 4′-tribromodiphenyl has been prepared from 4 : 4′-dibromo-2-nitrodiphenyl, in two stages. An attempt to obtain 2′ : 4 : 4′-tribromo-2-nitrodiphenyl by nitrating it under a number of different experimental conditions resulted in dinitration. The product appears to be 2′ : 4 : 4′-tribromo-3 : 5′-dinitrodiphenyl (V), since it reacts with hot piperidine to give a bromodinitrodipiperidinodiphenyl.

When the bisdiazonium perbromide was allowed to decompose in heated glacial acetic acid containing one molecular proportion of cinnamic acid or acetanilide or aceto-*p*-toluidide, 4 : 4′-dibromo-2-nitrodiphenyl but no tribromonitrodiphenyl was formed (cf. Bülow and Schmachtenburg, *Ber.*, 1908, **41**, 2607).

(V)



(VI)

The more general scope of the diazonium perbromide decomposition reaction has been examined in a number of cases: the perbromide derived from benzidine decomposed in boiling ethanol to give 4 : 4′-dibromodiphenyl, and in hot glacial acetic acid to give 2 : 2′ : 4 : 4′-tetrabromodiphenyl. That from 4-aminodiphenyl in boiling ethanol gave 4-bromodiphenyl, and in hot glacial acetic acid gave 4 : 4′-dibromodiphenyl. That from 2-nitro-*o*-tolidine in hot glacial acetic acid gave 4 : 4′-dibromo-3 : 3′-dimethyl-2-nitrodiphenyl (VI); this result was unexpected since the 2′-position should be more reactive than the corresponding position in the methyl-free compound. The perbromide from 4-aminodiphenyl ether in hot glacial acetic acid gave 4 : 4′-dibromodiphenyl ether.

Experimental

Bisdiazonium Perbromide from 2-Nitrobenzidine.—An improved method of preparing this compound was as follows: A solution of 2-nitrobenzidine (11·5 g.) in a hot mixture of 47% hydrobromic acid (72 g.) and water (144 c.c.) was cooled rapidly to about −2°. A solution of sodium nitrite (7·5 g.) in water (18 c.c.) was rapidly stirred into the paste, under the surface. After 10 min. the almost clear solution obtained was filtered and treated gradually, while being stirred, with a solution of bromine (8 c.c.) in 47% hydrobromic acid (50 c.c.). After 15 min. the orange-coloured diazonium perbromide was filtered off, washed with water, with absolute ethanol, and with dry ether and dried in a vacuum over solid potassium hydroxide and concentrated sulphuric acid (yield, 35·5 g., 96·5%).

Decomposition of the Bisdiazonium Perbromide.—(a) *In glacial acetic acid at* 95° ± 3°. The perbromide (7·33 g.) was added gradually to glacial acetic acid (40 c.c.) kept at 95° ± 3°. Then the solution was boiled until free from bromine. On cooling, a thick paste was obtained. Water was added to complete the separation of solid. The resulting paste was filtered off, washed with water, and dried at 100° and later in a vacuum (over H_2SO_4 and KOH) (yield,

3·85 g.) (Found: Br, 48·2. Calc. for $C_{12}H_6O_2NBr_3$: Br, 55·5. Calc. for $C_{12}H_7O_2NBr_2$: Br, 44·8%). By extracting twice with 50 c.c. of boiling light petroleum (b. p. 60—80°) this was freed from 4 : 4′-dibromo-2-nitrodiphenyl and gave 1·7 g. of 2′ : 4 : 4′-tribromo-2-nitrodiphenyl. Evaporation of the light petroleum extract gave 2·15 g. of almost pure dibromo-compound, which after crystallisation from ethanol had m. p. 124°, alone or mixed with 4 : 4′dibromo-2-nitrodiphenyl.

(b) *In glacial acetic acid containing* 4 : 4′*-dibromo-2-nitrodiphenyl.* The last experiment was repeated but with the initial addition of 3·57 g. (1 mol.) of 4 : 4′-dibromo-2-nitrodiphenyl. The yield of mixed products was 7·42 g., *i.e.*, 3·85 + 3·57 g.

(c) *In glacial acetic acid containing cinnamic acid or acetanilide or aceto-*p*-toluidide.* The perbromide was added to glacial acetic acid (at 100°) containing one of these substances (1 mol. for each mol. of perbromide). Routine methods led in each case to the isolation of 4 : 4′-dibromo-2-nitrodiphenyl, but no tribromonitrodiphenyl.

3′ : 4 : 4′*-Tribromo-2-nitrodiphenyl.*—3-Bromo-2′-nitrobenzidine (Lesslie and Turner, *J.*, 1933, 1590) was diazotised in hydrobromic acid solution at −4°. Addition of bromine in hydrobromic acid gave the yellow bisdiazonium perbromide. This was filtered off, washed with water, and dried in a vacuum. It was added gradually to glacial acetic acid kept at 100—110°. The solution was freed from bromine by boiling. On cooling, the *tribromonitro-compound* separated. After being crystallised from glacial acetic acid it formed leaflets, m. p. 141—142° (Found: Br, 55·0. $C_{12}H_6O_2NBr_3$ requires Br, 55·0%).

2-*Amino*-3′ : 4 : 4′*-tribromodiphenyl.*—A solution of the preceding nitro-compound in hot glacial acetic acid was treated with just over the calculated quantity of stannous chloride dissolved in concentrated hydrochloric acid. The mixture was boiled for a few minutes and then cooled, treated with excess of aqueous sodium hydroxide, and extracted with ether. The extract gave 2-*amino*-3′ : 4 : 4′*-tribromodiphenyl*, which crystallised from ethanol in needles, m. p. 78° (Found: Br, 58·8. $C_{12}H_8NBr_3$ requires Br, 59·0%).

2 : 3′ : 4 : 4′*-Tetrabromodiphenyl.*—(*a*) A solution of the aminotribromodiphenyl in glacial acetic acid was added gradually to a solution of sodium nitrite in concentrated sulphuric acid at 0°. The mixture was poured on ice and the solution obtained by filtration treated with bromine–hydrobromic acid. The precipitated perbromide was filtered off, washed, and dried in a vacuum (H_2SO_4). It was then gradually added to glacial acetic acid at 100°. The solution was freed from bromine by boiling and then cooled. The *tetrabromodiphenyl* which separated was crystallised from glacial acetic acid and formed needles, m. p. 124—125° (Found: Br, 67·5. $C_{12}H_6Br_4$ requires Br, 68·1%).

(*b*) 2 : 3′-Diamino-4 : 4′-dibromodiphenyl was diazotised in hydrochloric acid, and the bisdiazonium perbromide was precipitated in the usual way. It was decomposed in glacial acetic acid at 100°. The tetrabromodiphenyl obtained had m. p. 124—125° alone or when mixed with the product from (*a*).

2-*Amino*-2′ : 4 : 4′*-tribromodiphenyl.*—Reduction of the corresponding 2-nitro-compound, m. p. 195—196°, with stannous chloride in concentrated hydrochloric acid–glacial acetic acid, followed by normal procedure, gave the *base*, which after being crystallised from dilute alcohol (charcoal) and then from benzene formed rods, m. p. 154° (Found: Br, 58·8. $C_{12}H_8NBr_3$ requires Br, 59·1%).

2 : 2′ : 4 : 4′*-Tetrabromodiphenyl.*—(*a*) The foregoing base was diazotised by the acetic-sulphuric acid method and the diazonium perbromide formed and decomposed in the usual way. The *tetrabromo-compound* crystallised from glacial acetic acid as prisms, m. p. 273° (Found: Br, 68·2. $C_{12}H_6Br_4$ requires Br, 68·05%).

(*b*) 2 : 2′-Dibromobenzidine was diazotised and the bisdiazonium perbromide prepared, and then decomposed in hot glacial acetic acid. The tetrabromodiphenyl crystallised from the latter solvent in needles, m. p. 273° (Found: Br, 68·5%).

2-*Amino*-4 : 4′*-dibromo-2′-nitrodiphenyl.*—To a hot, well-stirred solution containing sulphur (1·6 g.), sodium sulphide (+9H_2O) (9·0 g.), and water (12 c.c.), was added an ethanolic solution of 4 : 4′-dibromo-2 : 2′-dinitrodiphenyl (10 g.). The solution was boiled for an hour, boiling water being added from time to time to maintain the volume. The solution was cooled and the orange-coloured precipitate filtered off. By extraction with dilute hydrochloric acid and precipitation with dilute aqueous ammonia and finally crystallisation from ethanol, 2-*amino*-4 : 4′*-dibromo-2′-nitrodiphenyl* was obtained as needles, m. p. 103—104° (Found: C, 39·8; H, 2·5; N, 7·7; Br, 42·7. $C_{12}H_8O_2N_2Br_2$ requires C, 40·0; H, 2·2; N, 7·6; Br, 43·0%).

2′ : 4 : 4′*-Tribromo-2-nitrodiphenyl.*—The foregoing base was diazotised by the acetic-sulphuric acid process. The diazonium perbromide was prepared, and decomposed in hot

glacial acetic acid. The tribromonitrodiphenyl obtained had m. p. 195—196°, alone or when mixed with the product from 2-nitrobenzidine.

2-Amino-4 : 4′-dibromodiphenyl.—4 : 4′-Dibromo-2-nitrodiphenyl was reduced in hot acetic–hydrochloric acid solution with stannous chloride. The cooled mixture was added to excess of dilute aqueous sodium hydroxide. The solid which separated was filtered off, washed with water, and crystallised from light petroleum (b. p. 60—80°) or from ethanol. The *2-amino-4 : 4′-dibromodiphenyl* formed needles, m. p. 130° (Found : Br, 48·7. $C_{12}H_9NBr_2$ requires Br, 48·9%).

2 : 4 : 4′-Tribromodiphenyl.—The foregoing base was diazotised by the acetic–sulphuric acid method. The diazonium perbromide was prepared and decomposed in hot acetic acid. The *tribromodiphenyl* obtained crystallised from ethanol in needles, m. p. 81° (Found : Br, 61·5. $C_{12}H_7Br_3$ requires Br, 61·4%).

Nitration of 2 : 4 : 4′-Tribromodiphenyl.—The tribromo-compound was dissolved in 10 parts of warm nitric acid (*d* 1·5). On cooling, a solid separated and this crystallised from ethanol in needles, m. p. 164—165° (Found : Br, 49·8. $C_{12}H_5O_4N_2Br_3$ requires Br, 49·9%). This is regarded as *2 : 4 : 4′-tribromo-3′ : 5-dinitrodiphenyl.* When heated with excess of piperidine for a few minutes it gave *2-bromo-3′ : 5-dinitro-4 : 4′-dipiperidinodiphenyl*(?), orange-red needles, m. p. 145—146°, from ethanol (Found : Br, 16·4. $C_{22}H_{25}O_4N_4Br$ requires Br, 16·4%).

2 : 4-Dibromoiodobenzene.—2 : 4-Dibromoaniline hydrochloride (29 g.) was diazotised in aqueous hydrochloric acid by aqueous sodium nitrite. The diazonium solution was added to potassium iodide solution and the solid which separated was steam-distilled from aqueous sodium hydroxide (yield, 27 g.). The dibromoiodobenzene crystallised from ethanol in needles, m. p. 45—46° (3·414 mg. gave 5·847 mg. of AgBr + AgI. Calc. for $C_6H_3Br_2I$: 5·759 mg.).

Bisdiazonium Perbromide from Benzidine.—Benzidine was diazotised in aqueous hydrochloric acid and the bisdiazonium perbromide precipitated in the usual manner, then decomposed as follows : (a) *In boiling ethanol.* The crude product after crystallisation from methanol had m. p. 164° and was identical with 4 : 4′-dibromodiphenyl. (b) *In glacial acetic acid at* 100°. The product, after crystallisation from glacial acetic acid, had m. p. 273° and was identical with 2 : 2′ : 4 : 4′-tetrabromodiphenyl.

Diazonium Perbromide from 4-Aminodiphenyl.—The perbromide, obtained in the usual way, was decomposed as follows : (a) *In boiling ethanol.* The product, after being crystallised from benzene, had m. p. 89° and was identical with 4-bromodiphenyl. (b) *In glacial acetic acid at* 100°. The product melted at 164°, after crystallisation from methanol, and was identical with 4 : 4′-dibromodiphenyl.

Bisdiazonium Perbromide from 2-Nitro-o-tolidine.—2-Nitro-*o*-tolidine was diazotised in hydrochloric acid and the bisdiazonium perbromide prepared in the usual manner. When it was decomposed in hot glacial acetic acid it gave *4 : 4′-dibromo-3 : 3′-dimethyl-2-nitrodiphenyl* which, after being crystallised from glacial acetic acid, formed needles, m. p. 240—241° (Found : Br, 42·2. $C_{14}H_{11}O_2NBr_2$ requires Br, 41·6%).

Diazonium Perbromide from 4-Aminodiphenyl Ether.—This was prepared in the normal manner. When decomposed in hot glacial acetic acid it gave 4 : 4′-dibromodiphenyl ether, which after being crystallised from ethanol had m. p. 60°.

BEDFORD COLLEGE, UNIVERSITY OF LONDON. [*Received, December 20th*, 1954.]

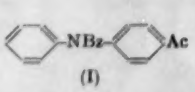
Some Derivatives of Diphenylamine.

By S. G. P. Plant and C. R. Worthing.

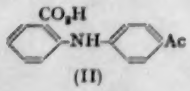
[Reprint Order No. 5985.]

4-Acetyldiphenylamine has been obtained by hydrolysis of the product of a Friedel–Crafts reaction with *N*-benzoyldiphenylamine, and by the decarboxylation of 4-acetyl-2′-carboxydiphenylamine. It has been converted into 4-carboxydiphenylamine by fusion with potassium hydroxide. The action of aniline on *o*-acetylphenyl toluene-*p*-sulphonate has been studied.

Friedel–Crafts reactions with carbazole and its *N*-alkyl and *N*-acyl derivatives, and the isomerisation of the *N*-acyl compounds with aluminium chloride, have given various *C*-acylcarbazoles from which the corresponding carbazolecarboxylic acids have been obtained on fusion with potassium hydroxide (see, *e.g.*, Plant and Williams, *J.*, 1934, 1142; Plant, Rogers, and Williams, *J.*, 1935, 741; Mitchell and Plant, *J.*, 1936, 1295). It seemed possible, therefore, that analogous derivatives of diphenylamine might be prepared in similar ways, but the results have been generally disappointing. Apart from *N*-benzoylation in some cases, attempts to introduce acetyl and benzoyl groups into diphenylamine and its *N*-acetyl and *N*-benzoyl derivatives have failed, except in the formation of 4-acetyl-*N*-benzoyldiphenylamine (I), a substance obtained by Chapman (*J.*, 1927, 1743) by rearrangement of *p*-acetylphenyl *N*-phenylbenzimidate. The constitution of this product was established by hydrolysis to 4-acetyldiphenylamine which was also prepared by the decarboxylation of 4-acetyl-2′-carboxydiphenylamine (II) obtained from *p*-aminoacetophenone and potassium *o*-bromobenzoate. It is of interest that Craig (*J. Amer. Chem. Soc.*, 1935, **57**, 195) obtained a small amount of 4-*tert.*-butyldiphenylamine



(I)



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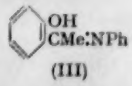

(III)

from diphenylamine and *tert.*-butyl chloride in the presence of aluminium chloride. The heating of *N*-acetyl- and *N*-benzoyl-diphenylamine with aluminium chloride failed to effect rearrangement (cf. Dippy and Wood, *J.*, 1949, 2719).

Fusion of 4-acetyldiphenylamine with potassium hydroxide gave 4-carboxydiphenylamine, prepared by Gilman and Brown (*J. Amer. Chem. Soc.*, 1940, **62**, 3208) by hydrolysis of the ester obtained by heating iodobenzene with methyl *p*-aminobenzoate. This product was shown to be identical (mixed m. p.) with the acid obtained by heating diphenylaminomagnesium iodide in a stream of carbon dioxide at 270° as described by Oddo (*Gazzetta*, 1911, **41**, 255). With the characterisation of the three possible carboxydiphenylamines the structure of Oddo's acid had become reasonably certain, but it appears hitherto not to have been rigidly proved.

In exploring another approach to 4-acetyldiphenylamine it was found that *p*-acetylphenyl toluene-*p*-sulphonate was little affected by boiling aniline. Similar treatment of *o*-acetylphenyl toluene-*p*-sulphonate gave a product which, although having the composition of 2-acetyldiphenylamine, was shown by its reactions to be *o*-(1-phenyliminoethyl)phenol (III). Thus it gave no 5-methylacridine on being heated with glacial acetic acid and a little concentrated sulphuric acid (cf. Jensen and Rethwisch, *J. Amer. Chem. Soc.*, 1928, **50**, 1144), it gave acetanilide on being shaken with acetyl chloride and alkali in acetone, it was hydrolysed to *o*-hydroxyacetophenone and aniline by boiling dilute hydrochloric acid, and the same compound was obtained by heating *o*-hydroxyacetophenone with aniline. It gave a deep reddish-brown colour with ethanolic ferric chloride, and it was soluble in 2N-hydrochloric acid, from which it was recovered by dilution with water, but it did not readily dissolve in dilute aqueous sodium hydroxide. Its structure affords the possibility of intramolecular hydrogen bonding, and this is reflected in its infrared spectrum in Nujol

suspension. Thus there is no absorption indicative of free hydroxyl in the region of 3μ, but there is a diffused broad band in the region of 4μ.

2-Acetyl-2′-carboxydiphenylamine was prepared from *o*-aminoacetophenone and potassium *o*-bromobenzoate, but attempts to convert it into 2-acetyldiphenylamine by decarboxylation failed. Most of the product was basic, and, although difficult to purify, it gave with concentrated sulphuric acid a yellow solution with a green fluorescence, indistinguishable from that obtained with 5-methylacridine.

It has not been possible to prepare 3-carboxydiphenylamine by fusion of 3-acetyldiphenylamine (Elson and Gibson, *J.*, 1931, 2381) with potassium hydroxide. This acid has been obtained in small yield by Gilman, Van Ess, and Shirley (*J. Amer. Chem. Soc.*, 1944, **66**, 1214) by hydrolysis of the product from the condensation of aniline with methyl *m*-iodobenzoate. A convenient alternative, although again with a small yield, is given below.

Experimental

4-Acetyl-2′-carboxydiphenylamine.—A stirred mixture of *p*-aminoacetophenone (13·5 g.), *cyclo*hexanol (140 c.c.), and potassium *o*-bromobenzoate (10·9 g.) with a little potassium iodide and copper powder was refluxed for 10 hr. After addition of dilute aqueous sodium hydroxide, the *cyclo*hexanol was removed in steam, and the residual solution cooled, filtered, and acidified with hydrochloric acid. *4-Acetyl-2′-carboxydiphenylamine* (6·5 g.; m. p. 160—164°) was obtained when the product was collected after 12 hr., stirred with its own volume of ethanol on a steam-bath for ½ hr., and the solid washed with a little ethanol. Recrystallisation from ethanol gave yellow prisms, m. p. 174° (Found: C, 70·7; H, 5·1. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·1%). Its *methyl ester* separated from methanol in pale yellow prisms, m. p. 80° (Found: C, 71·2; H, 5·9. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6%).

4-Acetyldiphenylamine.—(*a*) After the above acid (8 g.) had been heated at 250° until frothing ceased (1—2 hr.), the residue distilled at 235°/17 mm., and the distillate ground with hot ethanol (5 c.c.), *4-acetyldiphenylamine* (2·73 g.) was obtained. Recrystallisation from ethanol gave yellow needles, m. p. 112° (Found: C, 79·5; H, 6·3. $C_{14}H_{13}ON$ requires C, 79·6; H, 6·2%). In early preparations this substance was obtained in the less stable form of yellow prisms, m. p. 93°.

(*b*) After a stirred mixture of *N*-benzoyldiphenylamine (10 g.), carbon disulphide (70 c.c.), aluminium chloride (60 g.), and acetyl chloride (20 c.c.) had been refluxed for 5 hr., the solvent was distilled off, and the residue added to ice and dilute hydrochloric acid. When the product was crystallised from ethanol (charcoal), a pale yellow solid (7 g.), m. p. 120—132°, was obtained. This (5 g.) was twice recrystallised from carbon tetrachloride, from which 4-acetyl-*N*-benzoyldiphenylamine was isolated in pale yellow prisms (1·8 g.), m. p. 134—138°. A purer specimen, m. p. 136—138°, of the same substance (mixed m. p.) was obtained by adsorption of a little of the material, m. p. 120—132°, from benzene on alumina (Found: C, 79·7; H, 5·5; N, 4·8. Calc. for $C_{21}H_{17}O_2N$: C, 80·0; H, 5·4; N, 4·4%). After a solution of this benzoyl compound in an excess of aqueous ethanolic potassium hydroxide had been refluxed for 2½ hr. and poured into water, 4-acetyldiphenylamine, pale yellow needles, m. p. 109—110° (from carbon tetrachloride), identical (mixed m. p.) with the above ketone, was obtained.

A solution of 4-acetyldiphenylamine (0·5 g.) and a little (+)-camphorsulphonic acid in acetic anhydride (10 c.c.) was refluxed for 1½ hr. and poured into water (100 c.c.). The solid was purified by boiling its solution in ethanol with charcoal for 15 min. and recovered from the filtered liquid by evaporation to small bulk and precipitation with water. Crystallisation from carbon tetrachloride gave N: *4-diacetyldiphenylamine* (0·4 g.) in pale yellow prisms, m. p. 124° (Found: C, 75·9; H, 6·2. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0%). After its solution in aqueous ethanolic potassium hydroxide had been refluxed for 2 hr., addition of water precipitated 4-acetyldiphenylamine, identified by mixed m. p.

4-Acetyldiphenylamine (0·4 g.) in acetone (10 c.c.) was added to potassium hydroxide (2 g.) in water (1 c.c.), and the whole shaken for 15 min. with methyl sulphate (3 c.c.). When the product obtained by pouring the mixture into dilute aqueous potassium hydroxide was crystallised from methanol, *4-acetyl-N-methyldiphenylamine* (0·16 g.) separated in plates, m. p. 87° (Found: C, 79·8; H, 6·5. $C_{15}H_{15}ON$ requires C, 80·0; H, 6·7%).

4-Carboxydiphenylamine.—4-Acetyldiphenylamine (0·5 g.) was gradually stirred into a heated, molten mixture of potassium hydroxide (5 g.) and water (0·5 c.c.). When cold, the

whole was extracted with water and the filtered extract acidified with hydrochloric acid. The solid (0·13 g.; m. p. about 150°), after being boiled in ethanol with charcoal, was crystallised from benzene, from which 4-carboxydiphenylamine separated in plates, m. p. 158° (Found: C, 73·5; H, 5·3. Calc. for $C_{13}H_{11}O_2N$: C, 73·2; H, 5·2%).

o- *and* p-*Acetylphenyl Toluene*-p-*sulphonate*.—After a mixture of *o*-hydroxyacetophenone (30 g.), pyridine (90 c.c.), and toluene-*p*-sulphonyl chloride (64 g.) had been heated on a steam-bath for 2 hr. and left overnight, the whole was poured into dilute hydrochloric acid, and the product, which soon solidified, was washed with dilute aqueous sodium hydroxide. Crystallisation from ethanol gave o-*acetylphenyl toluene*-p-*sulphonate* (39 g.) in needles, m. p. 95—98° (Found: C, 61·8; H, 4·6; S, 11·3. $C_{15}H_{14}O_4S$ requires C, 62·1; H, 4·8; S, 11·0%). Its infrared spectrum in Nujol suspension contains a band at 5·89 μ, characteristic of the carbonyl group.

Prepared similarly from *p*-hydroxyacetophenone, p-*acetylphenyl toluene*-p-*sulphonate* separated from methanol in needles (23%), m. p. 72° (Found: C, 62·0; H, 4·6%).

o-(1-*Phenyliminoethyl*)*phenol*.—(*a*) After a mixture of *o*-acetylphenyl toluene-*p*-sulphonate (15 g.) and aniline (150 c.c.) had been refluxed for 24 hr. and poured into excess of dilute hydrochloric acid, the whole was extracted with ether and the extract shaken with dilute aqueous sodium hydroxide. When the solid obtained by acidification of the alkaline solution was crystallised from ethanol, toluene-*p*-sulphonanilide, m. p. 99—102°, identified by mixed m. p., was obtained. After the ethereal extract had been dried ($MgSO_4$) and evaporated, the residue was crystallised from ethanol and o-(1-*phenyliminoethyl*)*phenol* (3·48 g.) isolated in yellow plates, m. p. 84° [Found: C, 79·8; H, 6·2; N, 6·7%; *M* (Rast), 192. $C_{14}H_{13}ON$ requires C, 79·6; H, 6·2; N, 6·6%; *M*, 211].

(*b*) When *o*-hydroxyacetophenone (5 g.) was refluxed with aniline (30 c.c.) for 16 hr. and the mixture treated as above, *o*-(1-phenyliminoethyl)phenol (1·5 g.), identified by mixed m. p., was again obtained.

After *o*-(1-phenyliminoethyl)phenol (1 g.) in acetone (30 c.c.) had been added to potassium hydroxide (5·4 g.) in water (2·7 c.c.), the mixture was treated gradually with acetyl chloride (3 c.c.) in acetone (5 c.c.), and the whole shaken for ½ hr., diluted with water, and extracted with ether. The residue obtained when the extract was washed with aqueous alkali and with dilute hydrochloric acid, dried, and evaporated, was crystallised from carbon tetrachloride, from which acetanilide (0·25 g.), m. p. 114°, identified by mixed m. p., separated (Found: C, 70·9; H, 6·8. Calc. for C_8H_9ON: C, 71·1; H, 6·7%).

After *o*-(1-phenyliminoethyl)phenol (2·5 g.) had been refluxed for 2 hr. with hydrochloric acid (12%; 65 c.c.), the solution was diluted with water and extracted with ether. The material (1·3 g.) obtained from the ethereal extract was shown to be *o*-hydroxyacetophenone by conversion into *o*-acetylphenyl toluene-*p*-sulphonate as described above. The aqueous solution was shown to contain aniline by its conversion into acetanilide.

2-*Acetyl*-2′-*carboxydiphenylamine*.—Prepared from *o*-aminoacetophenone as described above for the isomeric compound, 2-*acetyl*-2′-*carboxydiphenylamine* (yield, 16%) separated from ethanol in golden yellow prisms, m. p. 207° (Found: C, 70·8; H, 5·4%).

N: 3-*Diacetyldiphenylamine*.—3-Acetyldiphenylamine (0·5 g.) in acetic anhydride (25 c.c.) containing a little (+)-camphorsulphonic acid was refluxed for 2½ hr. and poured into water. The product was extracted with ether, and the extract washed with aqueous sodium hydroxide, dried ($MgSO_4$), and evaporated. When the residue was crystallised from carbon tetrachloride, N: 3-*diacetyldiphenylamine* (0·37 g.) was obtained; recrystallisation from ethanol gave almost colourless prisms, m. p. 96—97° (Found: C, 75·7; H, 6·0%). When this compound was refluxed for 2 hr. with an excess of aqueous ethanolic potassium hydroxide and the solution poured into water, 3-acetyldiphenylamine was precipitated, having yellow prisms, m. p. and mixed m. p. 88—90° (from carbon tetrachloride).

3-*Carboxydiphenylamine*.—Aniline (150 c.c.), *m*-bromobenzoic acid (20 g.), and anhydrous sodium acetate (15 g.), with a little copper powder and potassium iodide, were refluxed for 24 hr., and the mixture, when cold, poured into an excess of hydrochloric acid (12%). The product was extracted with ether, and the extract filtered and shaken with dilute aqueous sodium carbonate. This aqueous layer was boiled for ½ hr. with charcoal, filtered, and acidified with hydrochloric acid. The precipitated material (7·5 g.; m. p. 137—145°) was refluxed for 20 hr. with methanol (400 c.c.) which had been saturated with hydrogen chloride, most of the solvent was distilled off, and the residue was treated with dilute ammonia solution. The product was collected in ether, the solution dried ($MgSO_4$), the solvent removed, and the residue crystallised from carbon tetrachloride, from which 3-*methoxycarbonyldiphenylamine* (1 g.)

separated in almost colourless plates, m. p. 110—112° (Found: C, 73·9; H, 5·8; N, 6·0. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·7; N, 6·2%). After the ester had been refluxed for 3 hr. with an excess of aqueous ethanolic potassium hydroxide, the solution was diluted, filtered, and acidified; 3-carboxydiphenylamine, needles, m. p. 139—141° (from benzene), was precipitated (Found: C, 73·0; H, 5·4%).

The authors are indebted to Dr. F. B. Strauss for infrared absorption spectra.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, December 20th, 1954.*]

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*Preparation of Phenothiazine Derivatives as Possible Anthelmintics. Part II.**

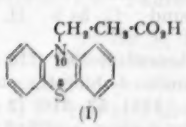
By ALEXANDER MACKIE and ANAND L. MISRA.

[Reprint Order No. 5845.]

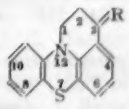
Some derivatives of 2 : 3-dihydro-3-oxo-1*H*-pyrido[3,2,1-*kl*]phenothiazine have been prepared.

SINCE β-10-phenothiazinylpropionic acid (I) showed distinct anthelmintic activity towards liver fluke *in vitro* (Mackie and Cutler, Part I *), it appeared desirable to prepare some derivatives of this acid, and also related compounds containing a ketomethylene group, which had been shown to induce anthelmintic activity *in vitro* (Mackie and Raeburn, *Brit. J. Pharmacol.*, 1952, **7**, 219).

Derivatives of 2 : 3-dihydro-3-oxo-1*H*-pyrido[3,2,1-*kl*]phenothiazine (II*a*) (Smith, *J. Org. Chem.*, 1950, **15**, 1125), *e.g.*, (II*b*), (II*c*), and (II*d*), have been prepared.

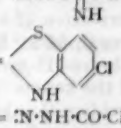


(I)



(II*a*), R = :O

(II*b*), R = :N·NH·C(:NH)·NH·NO₂

(II*c*), R = 

(II*d*), R = :N·NH·CO·CH₂·N⁺C₅H₅]Cl⁻

In an attempt to prepare β-10-phenothiazinylpropionyl chloride, for the purpose of lengthening the chain (Arndt–Eistert method), only the ketone (II*a*) could be obtained by the action of phosphorus oxychloride on the acid (I) or its sodium salt, or of phosphorus trichloride on the acid. Thionyl chloride gave an uncrystallisable gum. Reaction of the methyl ester with aqueous ammonia over a prolonged period or fusion of the acid (I) with urea (Cherbuliez and Landolt, *Helv. Chim. Acta*, 1946, **29**, 1438) did not produce the amide. Phenothiazine was isolated in the latter reaction. Phenothiazine was also obtained instead of the substituted benziminazole when the acid (I) was treated with *o*-phenylenediamine.

Bromination of the acid (I) in glacial acetic acid and acetic anhydride gave the monobromo-derivative of the ketone (II*a*), whilst similar bromination of the ketone (II*a*) appeared to give a difficultly separable mixture of its mono- and di-bromo-derivatives.

A quaternary hexamine salt was isolated from the reaction in chloroform of 10-chloroacetylphenothiazine (Dahlbom and Ekstrand, *Acta Chem. Scand.*, 1951, **5**, 102) with hexamine, recrystallisation of which resulted in decomposition to give hexamine hydrochloride as the only product isolated. Since it was considered that the introduction of the diethylaminoethylamino-group into a phenothiazine derivative containing a ketomethylene group might yield a compound showing anthelmintic properties (cf. Mauss *et al.*, *Naturwiss.*, 1946, **33**, 253; *Ber.*, 1948, **81**, 19), the chloro-compound was treated with 2-diethylaminoethylamine to form 10-2′-diethylaminoethylaminoacetylphenothiazine.

* Part I, *J.*, 1954, 2577.

For examination of the effect of a long continuous chain on *in vitro* anthelmintic activity, 10-phenothiazinylcarbonylmethyl stearate $C_{12}H_8SN{\cdot}CO{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}[CH_2]_{16}{\cdot}Me$ was prepared by condensing 10-iodoacetylphenothiazine (Dahlbom, *Acta Chem. Scand.*, 1953, **7**, 873) with sodium stearate.

Gilman and Nelson (*J. Amer. Chem. Soc.*, 1953, **75**, 5424) obtained 10-phenylacetylphenothiazine by condensing phenothiazine with phenylacetyl chloride in dioxan. When glacial acetic acid was used as the condensing medium, 10-acetylphenothiazine was isolated in good yield with the liberation of hydrogen chloride. 10-Phenylacetylphenothiazine gave phenothiazine and not 10-acetylphenothiazine when refluxed in glacial acetic acid saturated with hydrogen chloride. Chloroacetylation of phenothiazine was effected in dry benzene (Ekstrand, *Acta Chem. Scand.*, 1949, **3**, 302) and in dioxan (Gilman and Nelson, *loc. cit.*), but when glacial acetic acid was used as solvent 10-acetylphenothiazine resulted. It appears that phenylacetyl chloride and chloroacetyl chloride react in presence of glacial acetic acid to give the mixed anhydrides $CH_2Ph{\cdot}CO{\cdot}O{\cdot}COMe$ and $CH_2Cl{\cdot}CO{\cdot}O{\cdot}COMe$ respectively, which in turn react with the hydrogen chloride liberated, to give in each case acetyl chloride (Watson and Gregory, *J.*, 1929, 1373). This would explain the formation of acetylphenothiazine in these reactions, since phenothiazine is readily acetylated with acetyl chloride in glacial acetic acid. Condensation of phenothiazine with some aroyl chlorides, however, proceeds smoothly in glacial acetic acid (Part I).

Experimental

2 : 3-*Dihydro*-3-(*nitroamidinohydrazono*)-1H-*pyrido*[3,2,1-kl]*phenothiazine* (II*b*).—2 : 3-Dihydro-3-oxo-1*H*-pyrido[3,2,1-*kl*]phenothiazine (II*a*) (Smith, *J. Org. Chem.*, 1950, **15**, 1125) (4 g.) was added to a boiling glacial acetic acid solution of aminonitroguanidine (4 g. in 50 c.c.) (Phillips and Williams, *J. Amer. Chem. Soc.*, 1928, **50**, 2465) (cf. Whitmore, Revukas, and Smith, *ibid.*, 1935, **57**, 706). The mixture was heated for 0·5 hr., a yellow crystalline precipitate being formed. After cooling and filtration the residue was washed in turn with hot ethanol and ether, and dried. Recrystallisation from pyridine afforded golden-yellow plates of the *hydrazono*-derivative (2·5 g.), m. p. **234—235°** (decomp.) (Found: C, 54·3; H, 4·0. $C_{16}H_{14}O_2N_6S$ requires C, 54·2; H, 4·0%).

5′-*Chloro*-2 : 3-*dihydro*-1H-*pyrido*[3,2,1-kl]*phenothiazine*-3-spiro-2′-*benzothiazoline* (II*c*).—A pyridine solution of the ketone (II*a*) (2·6 g. in 5 c.c.) was added to 2-amino-4-chlorothiophenol hydrochloride in pyridine (Lankelma and Knauff, *J. Amer. Chem. Soc.*, 1931, **53**, 310) (2 g. in 5 c.c.). The mixture was refluxed on the water-bath for 8 hr., and after cooling, acidified with dilute hydrochloric acid. The supernatant liquid was decanted, and the red gum which remained was extracted in turn with ethanol and boiling light petroleum (b. p. 60—80°). The solid residue crystallised from acetone as scarlet shining needles of the spiro-*compound* (0·8 g.); m. p. 206—207° (Found: C, 64·0; H, 3·2. $C_{21}H_{15}N_3ClS_2$ requires C, 63·9; H, 3·8%) (cf. Lankelma and Sharnoff, *ibid.*, 1932, **54**, 379).

2 : 3-*Dihydro*-3-(*pyridinoacetylhydrazono*)-1H-*pyrido*[3,2,1-kl]*phenothiazine Chloride* (II*d*).—A suspension of the ketone (II*a*) (1·25 g.) and Girard reagent P (1 g.) in absolute ethanol (15 c.c.) containing 10% acetic acid was refluxed for 3 hr. The product which separated was filtered off, washed with hot absolute ethanol, and recrystallised from chlorobenzene–light petroleum (b. p. 40—60°) as yellow prisms (0·3 g.), m. p. 299—300° (Found: C, 70·6; H, 4·0; N, 10·3%). No definite structure could be assigned to this compound. Crystals separated from the filtrate after storage in ice overnight. These were recrystallised from ethanol–methanol, the *pyridinoacetylhydrazono*-compound being obtained as yellow stellate needles (0·7 g.), m. p. 192—194° (Found: N, 13·0. $C_{23}H_{19}ON_4ClS$ requires N, 13·3%).

Bromination of β-10-*phenothiazinylpropionic Acid*.—Bromine (2·9 g.) in glacial acetic acid (5 c.c.) was added to β-10-phenothiazinylpropionic acid (I) (Smith, *loc. cit.*) (5 g.), dissolved in a mixture of glacial acetic acid (30 c.c.) and acetic anhydride (10 c.c.). The temperature was kept at 40—50°. The mixture was then refluxed for 2 hr. on the water-bath; a yellow solid separated, which was collected and recrystallised from absolute ethanol. Dull yellow microscopic needles of ?-*bromo*-2 : 3-*dihydro*-3-*oxo*-1H-*pyrido*[3,2,1-kl]*phenothiazine* (1·5 g.), m. p. 247—248°, insoluble in aqueous sodium carbonate, were obtained (Found: C, 54·6; H, 2·9. $C_{15}H_{10}ONBrS$ requires C, 54·2; H, 3·0%).

10-(*Hexaminoacetyl*)*phenothiazine Chloride*.—A mixture of 10-chloroacetylphenothiazine

(Dahlbom and Ekstrand, *Acta Chem. Scand.*, 1951, **5**, 102) (3 g.) and hexamine (1·5 g.) in dry chloroform (15 c.c.) was refluxed on the water-bath for 5 hr. The colourless needles of the *quaternary salt* formed were filtered off, washed with chloroform, refluxed for 0·5 hr. with benzene, collected hot, and dried (3·3 g.), m. p. 172—173° (Found: C, 57·8; H, 5·6. $C_{20}H_{22}ON_6ClS$ requires C, 57·8; H, 5·3%). Recrystallisation of the quaternary salt from ethyl acetate–absolute ethanol afforded colourless prismatic needles of hexamine hydrochloride. m. p. 204—205° (decomp.) (Found: C, 40·9; H, 7·0. Calc. for $C_6H_{12}N_4,HCl$: C, 40·8; H, 7·4%; Locquin (*Bull. Soc. chim.*, 1900, **23**, 663) gives m. p. 188—189° (decomp.).

10-(2-*Diethylaminoethylaminoacetyl*)*phenothiazine*.—A mixture of 2-diethylaminoethylamine (6 g.) and 10-chloroacetylphenothiazine (5·5 g.) in dry benzene (30 c.c.) was refluxed on the water-bath for 10 hr. The resulting solution was shaken with N-hydrochloric acid, and the acid extract made alkaline with aqueous sodium carbonate. The *base*, which separated as an oil, solidified and was filtered off and dried. Recrystallisation from light petroleum (b. p. 40—80°) afforded colourless prisms of the pure base (2 g.), m. p. 79—80° (Found: N, 11·1. $C_{20}H_{25}ON_3S$ requires N, 11·8%) (cf. Dahlbom and Ekstrand, *loc. cit.*).

10-*Phenothiazinylcarbonylmethyl Stearate*.—A hot ethanolic solution of 10-iodoacetylphenothiazine (1·7 g. in 20 c.c.) (Dahlbom, *Acta Chem. Scand.*, 1953, **7**, 873) was added to an aqueous-ethanolic solution of sodium stearate (1·1 g. in 15 c.c.), made slightly acid to litmus. The mixture was refluxed on the water-bath for 3 hr. On cooling, the product was filtered off and recrystallised from ethanol in colourless plates of the *stearate* (1·6 g.), m. p. 73—74° (Found: C, 73·5; H, 8·2. $C_{32}H_{45}O_3NS$ requires C, 73·4; H, 8·6%).

The authors thank the Agricultural Research Council for financial aid, the Council of Scientific and Industrial Research (India) for the award of an Assam Oil Co. Scholarship to one of them (A. L. M.), Professor F. Bell for his interest, Dr. A. A. Cutler for assistance in the preparative work, and Dr. J. W. Minnis for some of the microchemical analyses.

HERIOT-WATT COLLEGE, EDINBURGH. [*Received, November 3rd*, 1954.]

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*Heterocyclic Fluorine Compounds. Part II.** Bz-*Monofluoroindoles.*

By F. L. ALLEN, J. C. BRUNTON, and H. SUSCHITZKY.

[Reprint Order No. 5904.]

The four *Bz*-monofluoroindoles have been made by a Fischer synthesis. 4- and 6-Fluoroindole were also prepared by an unequivocal method.

4-, 5-, 6-, and 7-FLUOROINDOLE have been prepared by a Fischer cyclisation of ethyl pyruvate *o*-, *m*-, and *p*-fluorophenylhydrazone, respectively, followed by hydrolysis and decarboxylation. The required hydrazones were obtained from the fluorophenylhydrazines (Suschitzky, *J.*, 1953, 3326), and also by a Japp–Klingemann reaction with the corresponding diazotised fluoroanilines. Ring closure of the *m*-fluorophenylhydrazone led to a mixture of ethyl 4- and 6-fluoroindole-2-carboxylate, the latter in large excess perhaps owing to the strong *para*-directing influence of fluorine; only the 6-fluoro-isomer could be isolated, the presence of the 4-fluoro-compound being inferred from the ultra-violet absorption.

Since authentic specimens of these two compounds were needed as reference compounds in the ambiguous cyclisation of ethyl pyruvate *m*-fluorophenylhydrazone, they were also made by an alternative route. Ethyl 6-fluoroindole-2-carboyxlate was obtained by a Reissert synthesis: condensation of 4-fluoro-2-nitrotoluene (*idem, loc. cit.*) with diethyl oxalate in the presence of potassium ethoxide afforded the potassium derivative of the keto-ester which, on alkaline reduction, yielded a mixture of the 6-fluoroindole acid and its ethyl ester. Ethyl 4-fluoroindole-2-carboxylate was made by a similar sequence of reactions. We failed to separate 2-fluoro-6-nitrotoluene, the starting material, from the nitration product of *o*-fluorotoluene by fractional distillation, as described by Schiemann (*Ber.*, 1929, **62**, 1794). It was readily obtained, however, by refluxing the nitration

* Part I, *J.*, 1953, 3845.

product in alcoholic potassium hydroxide (which converted the unwanted 2-fluoro-5-nitrotoluene into an ethyl ether), followed by fractionation. Cyclisation produced here only 4-fluoroindole-2-carboxylic acid. Treatment of its silver salt with ethyl iodide furnished the ester and an acidic by-product which agreed analytically with an ethyl-substituted monofluoroindolecarboxylic acid. We regard this compound as 3-ethyl-4-fluoroindole-2-carboxylic acid, because it possesses no ethylimino-group, and its nitroso-derivative gives a positive Liebermann's test (Verkade, Lieste, and Werner, *Rec. Trav. chim.*, 1945, **64**, 289).

Hydrolysis of the above esters followed by heating the resulting acids above their melting points yielded the four *Bz*-fluoroindoles. The use of lime for the decarboxylation (Ciamician and Zatti, *Ber.*, 1889, **22**, 197) gave poor yields.

Ultra-violet absorption maxima (mμ) in ethanol.

							Ethyl indole-2-carboxylate			
Indoles	λ_1	ε_1	λ_2	ε_2	λ_3	ε_3	λ_1	ε_1	λ_2	ε_2
4-F	216	42,000	265	5600	284·5	2000	232	29,000	287	17,000
5-F	218	22,000	280	6600	295·5	4100	218	20,000	291	19,500
6-F	216	33,000	275	5100	—	—	217	22,000	299	18,000
7-F	214	30,000	262	4300	285	2000	240	12,000		
							232	27,000	286	17,500

Data for the absorption spectra of both the fluorine-substituted indoles and monofluorocarbethoxy-indoles are given in the accompanying Table.

Experimental

Light petroleum had b. p. 60—80° and ligroin b. p. 80—100°. Ultra-violet spectra were determined in ethanol with a Unicam spectrophotometer S.P. 500.

Preparation of Ethyl Pyruvate Fluorophenylhydrazones.—(*a*) Equimolar quantities of ethyl pyruvate and the requisite fluorophenylhydrazine were heated together on a water-bath for 0·5 hr. The solid obtained on cooling was collected and crystallised from aqueous ethanol.

(*b*) A solution of diazotised *o*-, *m*- or *p*-fluoroaniline in concentrated hydrochloric acid (19 c.c.) and water (15 c.c.) was added to ethyl α-methylacetoacetate (7·2 g.) dissolved in 50% aqueous potassium hydroxide (17 c.c.) and ethanol (65 c.c.). Dilution of the red reaction mixture with water yielded a precipitate which was recrystallised from ethanol. The *ortho*-isomer separated first as a syrup, but crystallised in contact with ether. Mixed m. p.s of specimens from the two methods were undepressed.

Ethyl pyruvate o-fluorophenylhydrazone (38%), m. p. 113—114°, was obtained as pale yellow needles from chloroform–ligroin (1 : 1) (Found : N, 12·8. $C_{11}H_{13}O_2N_2F$ requires N, 12·5%); the meta-*isomer* (55%), colourless plates from ethanol, had m. p. 103° (Found : N, 12·2%), and the para-*isomer* [(*a*) 37%; (*b*) 55%], m. p. 90—91°, crystallised in colourless needles from aqueous ethanol (Found : N, 12·2%).

Cyclisation of Ethyl Pyruvate Fluorophenylhydrazones.—Each of the ethyl pyruvate fluorophenylhydrazones (4·5 g.) was cyclised in a boiling mixture of acetic acid (30 c.c.) and concentrated sulphuric acid (1·5 c.c.) during 5—15 min. Addition of water precipitated a crude product which was taken up in ether. After being washed free from acid (10% aqueous sodium carbonate) and dried ($MgSO_4$), the ethereal extract was evaporated to a nearly colourless solid. Ethyl pyruvate *m*-fluorophenylhydrazone gave a mixture of isomers which was first chromatographed (aluminium oxide; benzene–light petroleum, 10 : 1) and then fractionally crystallised (from light petroleum–benzene, 1 : 1). Ethyl 4-fluoroindole-2-carboxylate was obtained in an impure state from the isomeric mixture as the more strongly adsorbed and more soluble constituent, m. p. 108—112°, raised to 118° on admixture with an authentic specimen. Light absorption max. of the impure sample λ_1 233, λ_2 288 mμ (ε, 26,000; ε_2 16,500); this corresponds to *ca.* 75% of pure compound.

In another experiment a suspension of the silver salt (1·5 g.) of 4-fluoroindole-2-carboxylic acid (see below) in benzene was heated with ethyl iodide (1·0 g.) under reflux for 24 hr. The solid was filtered off, and the benzene solution, after extraction with sodium carbonate solution (10%) and drying ($MgSO_4$), yielded on evaporation *ethyl 4-fluoroindole-2-carboxylate* (38%) as white needles (from aqueous ethanol), m. p. 121° (Found : N, 6·5. $C_{11}H_{10}O_2NF$ requires

N, 6·8%). Acidification of the sodium carbonate extract gave a white solid (0·4 g.) of m. p. 205°, recrystallisable as needles from ethanol (Found: C, 63·7; H, 5·0; N, 7·0; NEt, 0%; equiv., 204·1. $C_{11}H_{10}O_2NF$ requires C, 63·8; H, 4·8; N, 6·8%; equiv., 207). Its nitroso-compound, prepared in glacial acetic acid by addition of sodium nitrite, gave a positive Liebermann reaction, and this substance is, therefore, regarded as *3-ethyl-4-fluoroindole-2-carboxylic acid*. Light absorption max.: **231** (ε 33,000) and 288 mμ (ε 13,000).

Ethyl 5-fluoroindole-2-carboxylate (65%) crystallised as needles (from ethanol), m. p. 148° (Found: N, 6·9%).

Ethyl 6-fluoroindole-2-carboxylate. (*a*) This *ester* was obtained pure from the mixture of isomers (see above) as the less adsorbed and less soluble constituent. When recrystallised from chloroform–light petroleum it had m. p. 143° (Found: N, 6·9%).

(*b*) 4-Fluoro-2-nitrotoluene (30 g.) (Suschitzky, *loc. cit.*; Steck and Fletcher, *J. Amer. Chem. Soc.*, 1948, **70**, 439) reacted with ethyl oxalate (24·6 g.) in ether (250 c.c.) in the presence of potassium ethoxide (from 7·8 g. of potassium and 55 c.c. of ethanol) at room temperature. After 48 hr. the red potassium salt (60%) was collected and dried. Acidification (dilute sulphuric acid and ether) of a portion of the salt gave *ethyl 4-fluoro-2-nitrophenylpyruvate*, m. p. 54°, as yellow needles (Found: N, 5·5. $C_{11}H_{10}O_5NF$ requires, N, 5·5%). The bulk of the potassium salt (29·3 g.), suspended in 460 c.c. of dilute aqueous ammonia (from 210 c.c. of solution of *d* 0·880), was reduced by adding a hot solution of ferrous sulphate (220 g.) in water (250 c.c.). The reaction mixture was boiled for 3 hr. and then filtered. Addition of acid to the filtrate deposited 6-fluoroindole-2-carboxylic acid (see below). The ethereal extracts of the iron residues gave ethyl 6-fluoroindole-2-carboxylate on evaporation as white leaflets (22%), m. p. 142—143°, unchanged on admixture with a sample obtained as in (*a*).

Ethyl 7-fluoroindole-2-carboxylate (50%) was obtained as white needles (from ethanol), m. p. 140° (Found: N, 7·0%).

Preparation of the Fluoroindoles-2-carboxylic Acids.—The ethyl esters above described were hydrolysed with aqueous-ethanolic sodium hydroxide. The acids were conveniently purified as their ammonium salts.

4-Fluoroindole-2-carboxylic Acid.—The isomeric mixture of nitro-compounds (89%) obtained by nitration of *o*-fluorotoluene (200 g.) (Schiemann, *loc. cit.*) was boiled under reflux for 1 hr. with aqueous-ethanolic 0·5N-potassium hydroxide (500 c.c.; 60% ethanol). Addition of brine precipitated an oil which was run off, washed with brine, and dried ($MgSO_4$). Fractionation gave 2-fluoro-6-nitrotoluene (10%; calc. on *o*-fluorotoluene), b. p. 91—92°/8 mm. (*idem*, *loc. cit.*, gives b. p. 97—97·2°/11 mm.). The residual liquid solidified and yielded nearly colourless needles of 2-ethoxy-5-nitrotoluene, m. p. 71° (from ethanol) (Found: N, 7·8. Calc. for $C_9H_{11}O_3N$: N, 7·7%). Staedel (*Annalen*, 1883, **217**, 153) records m. p. 71°. 2-Fluoro-6-nitrotoluene (15 g.) was caused to react with ethyl oxalate (17·3 g.) in the presence of potassium ethoxide as described for the preparation of ethyl 6-fluoroindole-2-carboxylate. Reductive ring-closure of the salt (19 g.) as before gave *4-fluoroindole-2-carboxylic acid* (2·3 g., 20%) as white needles (from aqueous ethanol), m. p. 219—220° (decomp.) (Found: N, 7·9%; equiv., 183. $C_9H_6O_2NF$ requires N, 7·8%; equiv., 179). Another 2 g. of this acid (17%) was obtained by extraction of the iron residues with ether followed by hydrolysis of the oily extract.

5-Fluoroindole-2-carboxylic acid (81%) recrystallised from aqueous ethanol as white needles, m. p. 248—249° (decomp.) (Found: N, 8·0%; equiv., 182).

6-Fluoroindole-2-carboxylic Acid.—(*a*) This acid formed leaflets (91%) (from aqueous ethanol), m. p. 246° (decomp.) (Found: N, 7·8%; equiv., 184).

(*b*) The acid (36%), prepared by a Reissert synthesis from 4-fluoro-2-nitrotoluene (see above), crystallised as white leaflets and had m. p. 245—246°, alone and mixed with the previous sample.

7-Fluoroindole-2-carboxylic acid (75%) was obtained as white leaflets, m. p. 198° (decomp.) (Found: N, 7·5%; equiv., 182).

Fluoroindoles.—The fluoroindolecarboxylic acids were heated above their m. p. until sublimation ceased (5—10 min.). Steam-distillation and recrystallisation furnished the colourless indoles.

4-Fluoroindole (80%) crystallised as white needles (from ligroin), m. p. 30° (Found: C, 71·6; H, 4·6; N, 10·5. C_8H_6NF requires C, 71·4; H, 4·5; N, 10·4%). It gave a *picrate* of orange-red needles (from benzene), m. p. 164—166° (Found: N, 15·3. $C_{14}H_9O_7N_4F$ requires N, 15·4%), and a *s-trinitrobenzene* derivative of orange-yellow needles (from ethanol), m. p. 172° (Found: N, 15·7. $C_{14}H_9O_6N_4F$ requires N, 15·5%).

5-Fluoroindole (52%), white leaflets (from ligroin), m. p. 46° (Found: C, 71·0; H, 4·5; N, 10·0%), gave a *picrate*, orange needles (from benzene), m. p. 155—156° (Found: N, 15·8%).

and a *s-trinitrobenzene* derivative, yellow needles (from ethanol), m. p. 160° (Found: N, 15·7%). The use of lime for the decarboxylation of this acid (Ciamician and Zatti, *loc. cit.*) gave a low yield (22%).

6-Fluoroindole. (*a*) The *compound* formed white needles (51%), m. p. 75°, from aqueous ethanol (Found: C, 71·0; H, 4·9; N, 10·0%), and gave a *picrate*, orange-red needles (from benzene), m. p. 147—148° (Found: N, 15·1%), and a *s-trinitrobenzene* derivative, orange-yellow needles (from ethanol), m. p. 151° (Found: N, 15·8%).

(*b*) 6-Fluoroindole-2-carboxylic acid (0·9 g.) and freshly prepared cuprous chloride (0·5 g.) were suspended in quinoline (25 c.c.) and refluxed for 3 hr. (Uhle, *J. Amer. Chem. Soc.*, 1949, **71**, 761). The mixture was poured on ice (150 g.) and concentrated hydrochloric acid (25 c.c.) and then extracted with ether. Evaporation of the ethereal layer furnished the acid as white needles (0·3 g., 44%), m. p. 74—75°.

7-Fluoroindole (48%) was obtained as white unstable crystals (from aqueous ethanol), m. p. 61—62° (Found: N, 10·7%). The *picrate* crystallised as orange-red needles, m. p. 154—155°, from benzene (Found: N, 15·7%).

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The Benzoin Reaction with Terephthalaldehyde.

By J. IDRIS JONES and P. B. TINKER.

[Reprint Order No. 5958.]

A polymer containing benzoin units is obtained by self-condensation of terephthalaldehyde. Certain of its derivatives have been prepared and on oxidation with nitric acid it gives a polymer containing benzil units.

THE benzoin condensation of dialdehydes appears to have been studied only by Grimaux (*Compt. rend.*, 1876, **83**, 826) and Oppenheimer (*Ber.*, 1886, **19**, 1814) who worked with terephthalaldehyde. A re-investigation of the product obtained in 90% yield by treatment of terephthalaldehyde with potassium cyanide has shown that it is polymeric. Although not of very high molecular weight, it is not the dimer $OHC{\cdot}C_6H_4{\cdot}CO{\cdot}CH(OH){\cdot}C_6H_4{\cdot}CHO$ as claimed by Oppenheimer. Its insolubility in most organic solvents has precluded precise determination of the chain length. The polymer is almost colourless and softens and melts at 170—200°, giving a viscous red liquid which sets on cooling to a brittle glass.

In the early stages of the reaction an intense red colour develops, which fades as reaction proceeds and is rapidly removed by treatment with acid and restored by alkali. The red colour is more persistent when the reaction is carried out in an atmosphere of nitrogen. These facts would find a ready explanation in terms of the coloured enediol (I) and colourless "benzoin" (II); however, stable dienols are known only for hindered 2:6-disubstituted benzoins (Ide and Buck, "Organic Reactions," Wiley, New York, 1948, Vol. IV, p. 269) and for the benzoin of pyridine-2-aldehyde where the dienol is stabilised by hydrogen bonding with the pyridine nitrogen atom (Hensel, *Angew. Chem.*, 1953, **65**, 491; Cramer and Krum, *Ber.*, 1953, **86**, 1586).

$$\text{(I)}\quad OHC{-}[{-}C_6H_4{\cdot}\underset{OH}{C}{=}\underset{OH}{C}{-}]_n{-}C_6H_4{\cdot}CHO \rightleftharpoons OHC{-}[{-}C_6H_4{\cdot}CO{\cdot}\underset{OH}{CH}{-}]_n{-}C_6H_4{\cdot}CHO \quad \text{(II)}$$

The analytical data for the polymer suggest that some oxidation, possibly of the aldehyde end-groups, also takes place during the reaction if the system is exposed to the atmosphere.

The polymer dissolved in concentrated aqueous alkali and from the product obtained on acidification some terephthalic acid was isolated (cf. the cleavage by alkali of benzoin; Sharpe and Miller, *J. Amer. Chem. Soc.*, 1952, **74**, 5643). This acid was obtained in good yield when an alkaline solution of the polymer was oxidised with hydrogen peroxide.

Oxidation with nitric acid furnished a bright yellow amorphous material with properties and elementary composition suggesting the structure $HO_2C{\cdot}[C_6H_4{\cdot}CO{\cdot}CO]_n{\cdot}C_6H_4{\cdot}CO_2H$. It had an indefinite melting point (~350°), was insoluble in the common solvents but soluble in aqueous alkali, formed derivatives with hydroxylamine and phenylhydrazine, and gave a colourless product on reductive acetylation.

Phthalaldehyde and *iso*phthalaldehyde appear to undergo condensations analogous to those of terephthalaldehyde.

Experimental

"Benzoin" Reaction of Terephthalaldehyde.—A few drops of potassium cyanide solution (10 g. in 20 ml.) were added to a 10% solution of the aldehyde (*Org. Synth.*, **20**, 92) in ethanol at room temperature. A red colour developed immediately and in a short time the solution became cloudy, a dark red precipitate then coagulating. This became colourless overnight, but was more readily decolorised when washed with very dilute acid. The product, obtained in 90% yield, was an off-white, amorphous solid softening and melting in the range 170—200°, almost insoluble in normal organic solvents, ethylene carbonate being the only solvent [Found: C, 70·0; H, 4·6. Calc. for $(C_8H_6O_2)_n$: C, 71·8; H, 4·4%]. If only the terminal aldehyde groups had been oxidised, the analysis approximates to that of a polymer comprising seven terephthalaldehyde units with two terminal carboxylic acid groups (Calc.: C, 70·0; H, 4·3%).

When the condensation was carried out in an atmosphere of nitrogen the red colour persisted for up to 20 hr. On addition of a few drops of mineral acid the colour changed to yellow and on addition of dilute sodium hydroxide solution this reverted to red. This change was reversible. Admission of air caused a gradual fading of the red colour. When the reaction was carried out under oxygen only a very pale red colour was observed.

The polymer dissolved in boiling phenylhydrazine. Pouring the solution into 2N-hydrochloric acid precipitated a yellowish-brown solid which dissolved in acetone and was reprecipitated by alcohol and water. It had an indefinite m. p. ~250° (Found: C, 74·5; H, 5·8; N, 6·0%). Partial conversion into a phenylhydrazone had taken place.

The polymer dissolved in aqueous caustic alkalis, and the concentration of the alkali solution did not seem to be critical. In 10% sodium hydroxide solution the material first blackened and dissolved, giving a clear red solution. On acidification a white solid was obtained from which some terephthalic acid was extracted and characterised as the dimethyl ester, m. p. 139°.

To the polymer (0·5 g.) dissolved in 5% sodium hydroxide solution (100 ml.), hydrogen peroxide (5 ml.; 30-vol.) was added and the solution was gently heated until it became colourless; then it was acidified. The product (0·5 g.) was shown to be terephthalic acid by conversion *via* the acid chloride into dimethyl terephthalate, m. p. 139° (0·4 g.).

Oxidation to the "Benzil" Polymer.—The aldehydic polymer (2 g.) was heated with water (1 ml.) and concentrated nitric acid (10 ml.) on a steam-bath for 2 hrs. Dissolution occurred and later a bright yellow compound was precipitated. More of this was obtained on dilution with water, giving a total yield of 90% (Found: C, 70·0; H, 3·3%). It had m. p. ~350° after preliminary charring and was insoluble in all organic solvents tried, including ethylene carbonate. It was not soluble in sodium hydrogen carbonate solution, but dissolved readily in sodium hydroxide solution giving a very dark solution. If the acid polymer has the structure suggested, a value $n = 5$ demands: C, 70·1; H, 3·1%, in close agreement with the values found. A value $n = 0$ (*i.e.*, for $C_{16}H_{10}O_8$) requires C, 64·4; H, 3·3%. Therefore the initial product is not the dimer postulated by Oppenheimer (*loc. cit.*).

The oxidised polymer dissolved in excess of hot phenylhydrazine, yielding, as above, a dull yellow amorphous product, m. p. ~260° after softening at 220°, soluble in acetone, less soluble in ethanol (Found: C, 73·2; H, 4·30; N, 11·6. A *monohydrazone* with $n = 5$ requires C, 73·6; H, 4·4; N, 11·2%).

An amorphous "oxime" (Found: N, 7·1%), m. p. 210—230°, was also obtained.

This work, published by permission of the Director of this Laboratory, was largely carried out by P. B. Tinker of the University of Sheffield under the vacation-student scheme of the Department of Scientific and Industrial Research in 1952. A complete study of the problem was not possible and it is not proposed to pursue the investigation.

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Elucidation of the Mechanism of the Michael Condensation with Oxygen-18 as Tracer. Part I. The "Abnormal" Reaction.

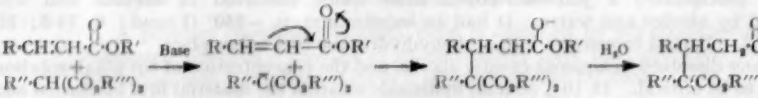
By DAVID SAMUEL and DAVID GINSBURG.

[Reprint Order No. 5835.]

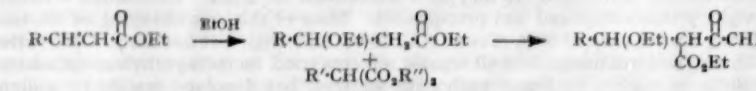
In the Michael condensations of dialkyl methylmalonates with ethyl crotonate or ethyl cinnamate, it has been shown, by using ^{18}O as tracer, that the "abnormal" reaction occurs with migration of the carboxyl group only. The isotopic results are consistent with the mechanism proposed by Lapworth for this reaction.

THE Michael condensation is the base-catalysed reaction between an "acceptor" compound containing an activated double or triple bond and a "donor" compound containing an active α-hydrogen atom, which results in the apparent addition of the component parts of the "donor" (proton and carbanion) to the multiple bond of the "acceptor." It is believed at present that the carbanion formed from the "donor" in alkaline solution attacks the more positive end of the polarised system of the "acceptor," yielding an anion which after treatment with water yields the ultimate adduct. (For a fuller discussion, see Bergmann, Ginsburg, and Pappo, "The Michael Condensation," in "Organic Reactions," Wiley, New York, in the press).

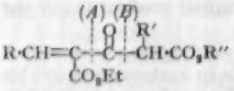
The Michael condensation may be exemplified by the following reaction scheme:



It has been suggested, however, that the first stage of the process may not necessarily be the formation of the new carbon–carbon bond, but rather a condensation of the Claisen type between the "acceptor" which has been modified for this purpose through the addition of ethanol across the double bond and the carboxylate group of the "donor" (Shafer, Loeb, and Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 5963; personal discussion with Professor Johnson in New Hampshire, August, 1954):



Subsequently, by concerted alcoholysis at either (*A*) or (*B*) and addition of the remaining fragment to the regenerated double bond, the reaction product is obtained.

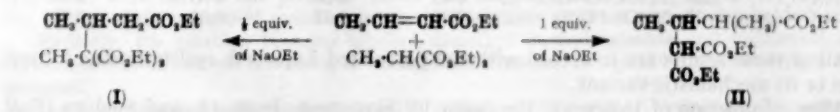


In order to elucidate the mechanism of the Michael condensation, it was felt, therefore, that the use of ^{18}O as tracer would furnish much information as to the intimate course of the reaction, since the functional groups of the "donor," "acceptor," solvent, and catalyst, all contain oxygen.

Since debate has been raging for some decades regarding the mechanism of the Michael condensation (see, *e.g.*, Thorpe, *J.*, 1900, **77**, 923; Michael and Ross, *J. Amer. Chem. Soc.*, 1930, **52**, 4598; Farmer, Ghosal, and Kon, *J.*, 1936, 1804; Holden and Lapworth, *J.*, 1931, 2368; Michael, *J. Org. Chem.*, 1938, **2**, 303), it was decided to select as the subject of this investigation those reactions chiefly involved in these polemics (Michael, *Ber.*, 1900, **33**, 3731; Michael and Ross, *loc. cit.*; Holden and Lapworth, *loc. cit.*).

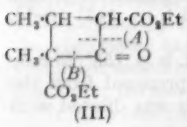
When ethyl crotonate is treated with diethyl methylmalonate in the presence of one-sixth of an equivalent of sodium ethoxide, the so-called "normal" product (I) is obtained.

When, however, a full equivalent of sodium ethoxide is used, the so-called " abnormal " product (II) results. It is this reaction which has caused much of the confusion in the literature. In this communication we report our isotopic results for the " abnormal " reactions of esters of methylmalonic acid with ethyl crotonate and with ethyl cinnamate.



The formulation proposed by Michael and Ross (*loc. cit.*; cf. Thorpe, *J.*, 1900, **77**, 932) to account for the structures of the products when different quantities of sodium are used is that, when one-sixth of an equivalent of sodium is used, the " donor " adds to the double bond of the " acceptor " in form of the components $H \cdots CMe(CO_2Et)_2$, whilst when a full equivalent of sodium is used, the " donor " breaks up into the components $Me \cdots CH(CO_2Et)_2$. Such a formulation, proposed for the splitting of sodiomethyl cyanoacetate in 1900, is inconsistent with present-day knowledge of base-catalysed ionic or free-radical mechanisms in organic chemistry. The portion of the Michael condensation adducts resulting from the crotonate precursor is indicated by the heavy type in the above formulæ (I and II) : thus, if a rearrangement is involved in this base-catalysed reaction, it is more plausible to assume that the ethoxycarbonyl group migrates and not the methyl group.

Holden and Lapworth (*loc. cit.*) have, indeed, presented a formulation which explains the means through which migration of an ethoxycarbonyl group can occur. They assumed that an intermediate *cyclo*butanone (III) is obtained. If alcoholysis of this postulated but unisolated intermediate of intramolecular Dieckmann condensation occurs at (*A*), the " normal " adduct is obtained. If, on the other hand, alcoholysis occurs at (*B*), the " abnormal " product results. Johnson's suggestion avoids the necessity for assuming even the transient existence of this strained intermediate and explains the results obtained in certain other " abnormal " Michael condensations (Shafer, Loeb, and Johnson, *loc. cit.*).



(III)

Using ^{18}O as tracer in the carboxyl group, we have shown, labelling each component separately, that, both for crotonate and for cinnamate, " abnormal " reaction occurs with migration of the carboxyl group only. Dimethyl [$^{18}O_4$]methylmalonate (all four oxygen atoms isotopically enriched) was condensed with unlabelled ethyl crotonate in the presence of one equivalent of sodium, under the exact conditions described by Michael and Ross (*loc. cit.*). The resulting triester was hydrolysed with aqueous sodium hydroxide; the free acid was extracted but had to be purified by recrystallisation as, in analogy to the work of Tsuruta, Yasuhara, and Furukawa (*J. Org. Chem.*, 1953, **18**, 1246), here also mixtures of " normal " and " abnormal " esters were obtained. However, there is no doubt that the " abnormal " product predominated.

Since *n*-alkyl esters of carboxylic acids are hydrolysed by acyl–oxygen fission (Polanyi and Szabo, *Trans. Faraday Soc.*, 1934, **30**, 508; Datta, Day, and Ingold, *J.*, 1939, **838**; Samuel, unpublished results) the ethoxyl oxygen atoms of the ethoxycarbonyl groups are lost on hydrolysis. Separate experiments showed that no exchange between the oxygen of the carbonyl group and the solvent occurred on hydrolysis or working up (cf. Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626). The tricarboxylic acid was then decarboxylated at 200° and the resulting carbon dioxide was introduced directly into the mass spectrometer. The ratio of mass **46** to mass **44** was determined and the atom % excess of ^{18}O calculated.

The results are tabulated together with the atom % excess of ^{18}O calculated by assuming migration of an ethoxycarbonyl group, and, for comparison, with the atom % excess of ^{18}O calculated by assuming the Thorpe–Michael methyl migration. It should be noted that no isotope effects in the decarboxylation were evident.

Similarly, the results for the " abnormal " reaction of ethyl [^{18}O]crotonate and unlabelled diethyl methylmalonate and for dimethyl [$^{18}O_4$]methylmalonate and unlabelled ethyl cinnamate, are given in the Table.

Atom % excess ^{18}O in " abnormal " Michael condensation.

Reactants	^{18}O in labelled reactants	Found	Calc. for CO_2H migration	Calc. for Me migration
$Me{\cdot}CH(C^{18}O_2Me)_2$ + $Me{\cdot}CH{:}CH{\cdot}CO_2Et$ ...	1·68	0·52	0·42	1·68
$Me{\cdot}CH(CO_2Et)_2$ + $Me{\cdot}CH{:}CH{\cdot}C^{18}O^{18}OEt$ ...	0·43	0·10	0·10	0·00
$Me{\cdot}CH(C^{18}O_2Me)_2$ + $Ph{\cdot}CH{:}CH{\cdot}CO_2Et$ ...	0·88	0·22	0·22	0·88

All of these results are in accord with the postulated Lapworth *cyclo*butanone formulation or its mechanistic variant.

After completion of this work, the paper by Simamura, Inamoto, and Suehiro (*Bull. Chem. Soc. Japan*, **1954**, **27**, 221) came to our attention. These workers concluded that in the " abnormal " reaction between ethyl [*carboxy*-^{14}C]-crotonate and diethyl methylmalonate, it is the ethoxycarbonyl group that migrates. Our conclusions are in full accord with these results, but as stated above, the use of ^{18}O in this case appears to afford a tool for the investigation of the various other aspects of the Michael condensation. Our further conclusions regarding the mechanism of the " normal " reaction will be reported in a subsequent publication.

Experimental

Preparation of Unlabelled Materials.—Diethyl methylmalonate was prepared (81% yield) according to *Org. Synth.*, Coll. Vol. II, p. 279, procedure B, Wiley, New York; it had b. p. 197°.

Ethyl crotonate was prepared by keeping crotonic acid (50 g.) in absolute ethanol (200 ml.) and concentrated sulphuric acid (2 ml.) for 24 hr. at room temperature. The mixture was then worked up as described by Michael (*Ber.*, 1900, **33**, 3766); the ester had b. p. 143° (yield, 60 g., 75%).

Ethyl cinnamate was redistilled Eastman Kodak " white label " material, b. p. 158°/25 mm.

Preparation of Labelled Materials.—A 5N-$Na^{18}OH$ stock solution was prepared from the required amount of 3% sodium amalgam and water enriched in ^{18}O. This was diluted with enriched water as required.

N-Sulphuric acid was prepared from the required amount of concentrated sulphuric acid and water enriched in ^{18}O.

Dimethyl [^{18}O]*Methylmalonate.*—[$^{18}O_4$]Methylmalonic acid was prepared by two methods. (*a*) Methylmalononitrile (2·4 g.), prepared from α-bromopropionic acid according to the method of Strack and Schwaneberg (*Ber.*, 1934, **67**, 41), was refluxed with 5N-$Na^{18}OH$ (13 ml.) until there was no further evolution of ammonia. Calcium chloride (4 g.) was then added to the hot solution, and the precipitate of calcium methylmalonate was removed by filtration and then washed alternately with hot water and cold water and finally with ether. The dry salt (4·7 g.) was then suspended in dry ice-cold ether (about 10 ml.), and concentrated hydrochloric acid (5 ml.) was added with cooling and stirring. The ether solution was separated, washed once with saturated aqueous sodium sulphate (2 ml.), and dried (Na_2SO_4). On removal of the ether, colourless [$^{18}O_4$]methylmalonic acid, m. p. 139°, was obtained (3·5 g.). Owing to the low yields of methylmalononitrile obtained by us according to the somewhat ambiguous directions of Strack and Schwaneberg, further quantities of labelled methylmalonic acid were obtained by method (*b*).

(*b*) Diethyl methylmalonate was refluxed with a slight excess of N-$Na^{18}OH$ until a homogeneous solution was obtained. The aqueous solution was extracted once with ether, then brought to the b. p. and the calculated amount of calcium chloride was added to precipitate the calcium methylmalonate. The salt was worked up as described above. The methylmalonic acid obtained in this manner was also labelled in all four oxygen atoms but with an atom % excess of ^{18}O one-half of that of the water used.

An ether solution of methylmalonic acid obtained by either method was then esterified with diazomethane. On distillation, dimethyl [$^{18}O_4$]methylmalonate, b. p. 75°/11 mm., was obtained.

Ethyl [^{18}O]*Crotonate.*—Ethyl crotonate (30 g.) was refluxed in 1N-sulphuric acid enriched in ^{18}O (30 ml.) for 7 days. The aqueous suspension was extracted with ether (3 times), and the extract was washed with water and dried (Na_2SO_4). On removal of the ether, colourless crystals of [$^{18}O_2$]crotonic acid, m. p. 74°, were obtained. In addition to the labelled oxygen atom introduced by hydrolysis, slow exchange between the free carboxyl group and the ^{18}O-enriched acid medium also increases the enrichment of the crotonic acid. Esterification was

accomplished as describedabove for the unlabelled acid. Distillation afforded ethyl [*carbonyl*-^{18}O]-crotonate, b. p. 143° (35 g.).

Michael Condensations.—The reactions between unlabelled diethyl methylmalonate and labelled ethyl crotonate, and between labelled dimethyl methylmalonate and unlabelled ethyl crotonate, were carried out precisely under the conditions described by Michael and Ross (*loc. cit.*, p. 4605), using 0·05 molar quantities. The yields reported were duplicated.

Similarly, the reaction between labelled dimethyl methylmalonate and unlabelled ethyl cinnamate was carried out according to Michael and Ross (*loc. cit.*, p. 4609) but a lower yield was obtained.

The triesters in each case were hydrolysed by refluxing with N-sodium hydroxide. The mixtures were then chilled, covered with ether, and carefully acidified by dropwise addition of hydrochloric acid with stirring and ice-cooling. The ether was removed and the acids were recrystallised to constant m. p. and isotopic content from a mixture of light petroleum, chloroform, and ether. α-Carboxy-βγ-dimethylglutaric acid formed crystals, m. p. 145°. α-Carboxy-γ-methyl-β-phenylglutaric acid formed crystals, m. p. 145°. Michael and Ross (*loc. cit.*) report m. p. 145° for both acids.

Mass-spectrometric Analyses of Reactants and Products.—Ethyl crotonate was hydrolysed with excess of N-sodium hydroxide, the solution was made exactly neutral with N-nitric acid, excess of silver nitrate was added, and N-sodium hydroxide was added dropwise until the white precipitate retained a brownish tinge. The silver crotonate was removed by filtration, washed with water, and dried in a vacuum. A sample (0·1 g.) was decarboxylated at 400° in the gas-inlet system of the mass spectrometer.

Dimethyl methylmalonate was hydrolysed with a slight excess of N-sodium hydroxide, the calcium salt was isolated, and the free acid obtained as described above. The acid was decarboxylated at 160° in the gas-inlet system of the mass spectrometer.

α-Carboxy-βγ-dimethylglutaric acid and α-carboxy-γ-methyl-β-phenylglutaric acid were decarboxylated in sealed tubes with break-off tips. Samples of approx. 0·01 g. were heated in evacuated sealed tubes to 200°. The sealed tubes were then opened by a magnet-operated iron breaker in the gas-inlet system of the mass spectrometer.

In each case the ratio of mass 46 to mass 44 was determined and the atom % excess of ^{18}O given in the Table was calculated.

Tests of Exchange and Working Up.—The following experiments were performed in order to determine whether any change in ^{18}O content occurred on isolation of the products or in preparation and decarboxylation of the samples: (*a*) Unlabelled methylmalonic acid was decarboxylated in sealed tubes. The results showed that no significant isotope effect occurs on decarboxylation and that no other products of masses 44 or 46 are produced. (*b*) Glutaric acid was heated to 200° with carbon dioxide enriched in ^{18}O in a sealed tube. No decrease in atom % excess of ^{18}O in the carbon dioxide occurred. This indicates that no direct exchange, or decarboxylation or dehydration of the glutaric acid, occurred. (*c*) Unlabelled methylmalonic acid was refluxed with N-Na^{18}OH for 48 hr. The acid was then isolated and analysed as described above. No exchange between the methylmalonate ion and the solvent was detected. (*d*) Methylmalonic acid enriched in ^{18}O was esterified with diazomethane. The ester was hydrolysed with N-sodium hydroxide solution, and worked-up as described above. The enrichment of the carbonyl-^{18}O before esterification and after working up remained unchanged.

We thank Dr. Israel Dostrovsky for helpful discussion during this work.

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Dithiols. Part XV. Some Polyhydroxy-derivatives of 3 : 4-Dimercaptobutanol.*

By N. S. Johary and L. N. Owen.

[Reprint Order No. 5919.]

3 : 4-Dimercaptobutyl β-D-glucoside and D-mannitol 1- and D-glucitol 6-(3 : 4-dimercaptobutyl) ether have been synthesised as their fully acetylated derivatives; there is evidence for partial cyclisation during deacetylation. The secondary ether linkage in the 3-(but-3-en-1-yl) ether of D-mannitol is very readily cleaved by aqueous acid; the isomeric primary 1-ether also undergoes fission, though more slowly.

During deacetylation of the acetylated glucoside and hexitol ethers of 2 : 3-dimercaptopropanol ("BAL"), cyclisation between one of the thiol groups and a hydroxy-group in the polyhydroxy-portion may occur to a small extent; the smallest possible ring for such an intramolecular cyclic sulphide would be six-membered (see Harding and Owen, *J.*, 1954, 1536). Interposition of an extra methylene group in an appropriate position would make the smallest possible ring seven-membered, and cyclisation might therefore occur less readily. It was with this possibility in mind that the derivatives of 3 : 4-dimercaptobutanol, described below, were prepared. The methods were essentially similar to those used for the corresponding 2 : 3-dimercaptopropyl compounds (Evans and Owen, *J.*, 1949, 244; Bladon and Owen, *J.*, 1950, 591).

Interaction of acetobromoglucose and but-3-en-1-ol (conveniently prepared by semi-hydrogenation of but-3-yn-1-ol) gave but-3-en-1-yl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (I), which with bromine furnished the 3 : 4-dibromobutyl compound (II); this, on reaction with potassium thiolacetate, gave 3 : 4-bisacetylthiobutyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (III).

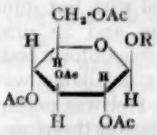
Ring fission of 5 : 6-anhydro-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-mannitol with but-3-en-1-ol in the presence of its sodium derivative gave the 6-(but-3-en-1-yl) ether (IV). This was hydrolysed to crystalline 1-*O*-(but-3-en-1-yl)-D-mannitol, which was converted into the solid penta-acetate (V). Treatment with bromine then gave a semi-solid product from which a crystalline dibromide (VI) was separated; this was probably one stereochemically pure form of the two possible diastereoisomeric dibromides which arise because of the introduction of a new centre of asymmetry at this stage. The liquid residue on fractional distillation gave some oily dibromide, together with an unexpected crystalline bromine-free product which was identified as hexa-*O*-acetylmannitol; this probably arose by slight fission, at an earlier stage, of the butenyl ether linkage (see below). Reaction of the crystalline dibromide (VI) with potassium thiolacetate gave 1 : 2 : 3 : 4 : 5-penta-*O*-acetyl-6-*O*-(3 : 4-bisacetylthiobutyl)-D-mannitol (VII).

The stereoisomeric sorbitol compound (VIII) was obtained by a similar series of reactions from 5 : 6-anhydro-1 : 3-2 : 4-di-*O*-ethylidene-D-glucitol. In this series no crystalline products were isolated with the exception of a by-product, $C_{34}H_{40}O_{11}$, which accompanied the 6-*O*-(but-3-en-1-yl)-1 : 3-2 : 4-di-*O*-ethylidene-D-glucitol and was probably the intermolecular ether (IX) formed by further reaction between the anhydro-compound and the free 5-hydroxyl group in the main product.

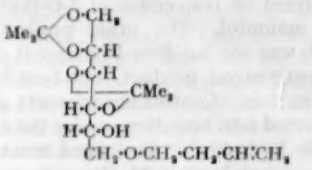
3-*O*-(But-3-en-1-yl)-1 : 2-5 : 6-di-*O*-*iso*propylidene-D-mannitol was prepared by mono-etherification of 1 : 2-5 : 6-di-*O*-*iso*propylidene-D-mannitol with but-3-en-1-yl bromide and sodium hydroxide in aqueous dioxan. When this was subjected to acid hydrolysis to remove the *iso*propylidene residues, under conditions similar to those used in the preparation 3-*O*-allyl-D-mannitol (Bladon and Owen, *loc. cit.*), the main product was mannitol, and to obtain the desired 3-*O*-(but-3-en-1-yl)-D-mannitol it was necessary to hydrolyse the di-*iso*propylidene compound by much milder treatment; this remarkable sensitivity of the butenyl group is discussed further on p. 1294. When the crystalline 3-butenyl ether was acetylated it gave a liquid penta-acetate which probably contained a small proportion of

* Part XIV, Harding and Owen, *J.*, 1954, 1536.

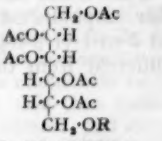
hexa-*O*-acetylmannitol, since it did not take up the theoretical amount of bromine and the crude dibromide on distillation gave some lower-boiling material from which hexa-*O*-acetylmannitol was isolated. It seems likely, therefore, that slight fission of the butenyl ether linkage occurs even during acetylation, though it was not possible to isolate any of the hexa-acetyl compound at that stage owing to an insufficient difference between its boiling point and that of the penta-acetyl ether; after bromination, the difference was enough for some separation to be possible. Owing to the small amount of pure dibromide which was now available, only an impure thiolacetate was obtained in this series.



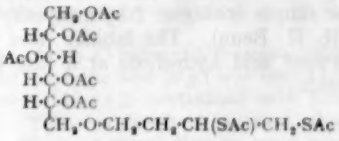
(I; R = $-CH_2\cdot CH_2\cdot CH{:}CH_2$)
(II; R = $-CH_2\cdot CH_2\cdot CHBr\cdot CH_2Br$)
(III; R = $-CH_2\cdot CH_2\cdot CH(SAc)\cdot CH_2\cdot SAc$)



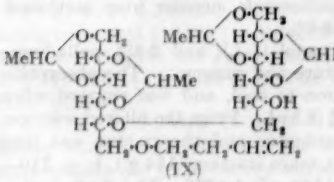
(IV)



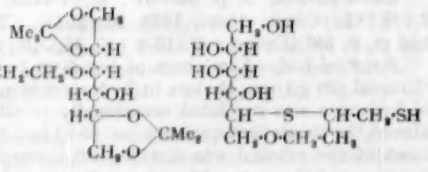
(V; R = $-CH_2\cdot CH_2\cdot CH{:}CH_2$)
(VI; R = $-CH_2\cdot CH_2\cdot CHBr\cdot CH_2Br$)
(VII; R = $-CH_2\cdot CH_2\cdot CH(SAc)\cdot CH_2\cdot SAc$)



(VIII)



(IX)



(X) (XI)

Deacetylation of the acetylthio-compounds (III), (VII), and (VIII) was carried out by the usual method with methanolic barium methoxide, which also precipitates the liberated dithiol as the barium salt. Previous experience has shown that owing to their extreme sensitivity towards oxidation, particularly when in contact with solvent, complete purification of these salts is impracticable. The crude material, however, is stable when thoroughly dried, and aqueous solutions for pharmacological tests can conveniently be prepared by precipitation of barium as sulphate and determination of thiol content in the buffered filtrate by titration with iodine. The quality of the salt is most usefully assessed by the ratio of thiol-sulphur to total sulphur, any deficiency from unity being a measure of the amount of cyclisation or of oxidation. The ratio 0·79 for barium salt derived from the glucoside (III) was about the same as that observed in many preparations of its lower homologue, though when the highly purified crystalline hexa-acetyl derivative was used, as a control, the derived barium salt of BAL-glucoside showed a ratio of 0·89. The barium salt from the mannitol ether (VII) was of much better quality (ratio, 0·89) than that (ratio, 0·46) from the stereoisomeric sorbitol compound, probably because the former ether (VII) was prepared from a crystalline dibromide, whereas in the sorbitol series all the intermediates were high-boiling viscous liquids which could not be rigorously purified. Pharmacological tests, kindly carried out by Dr. K. Adam, on the *O*-glucoside of 3 : 4-dimercaptobutanol prepared from the above barium salt showed its therapeutic efficiency against arsenical poisoning to be slightly less than that of BAL-glucoside.

Deacetylation of the ether (VII) was also studied under acid conditions but, although 86% of the theoretical thiol value was attained in boiling methanolic hydrogen chloride, the material obtained on evaporation of the solution contained less than half its total sulphur as free thiol; it afforded a crystalline substance which from the analytical data was probably an anhydro-derivative involving one of the sulphur atoms, such as (XI). Abnormal results of deacetylation under acidic conditions have been encountered before, and were tentatively attributed to the formation of cyclic sulphides (Miles and Owen, *J.*, 1952, 817).

The unexpected fission of the butenyl ether linkage in the hydrolysis of (X) was confirmed by conversion of 3-*O*-(but-3-en-1-yl)-D-mannitol with hot dilute sulphuric acid into mannitol. The other products included butadiene and an unsaturated alcohol which was not but-3-en-1-ol since it gave a strongly positive iodoform test; it was possibly the rearranged product, but-1-en-3-ol, but the quantity available was insufficient for purification. Control experiments showed that but-3-en-1-ol was neither isomerised nor converted into butadiene under the conditions used; the fission therefore does not involve simple hydrolysis. Prolonged treatment of the 6-*O*-(but-3-en-1-yl) ether (IV) with hot aqueous sulphuric acid also gave some mannitol and butadiene, but the primary ether linkage was markedly more stable than the secondary. Fission has also been observed in the simple analogue, 2-hydroxyethyl but-3-en-1-yl ether (unpublished experiments by Mr. M. H. Benn). The lability does not extend to but-3-en-1-yl β-D-glucoside, which underwent acid hydrolysis at a rate not significantly different from that of allyl β-D-glucoside.

Experimental

Light petroleum refers to the fraction of b. p. 40—60°, unless otherwise stated.

But-3-yn-1-ol, b. p. 60—61°, n_D^{21} 1·4403, was prepared by Kreimeier's method (U.S.P. 2,106,182; *Chem. Abstr.*, 1938, **32**, 2547). The 3 : 5-*dinitrobenzoate*, needles from methanol, had m. p. 58° (Found : N, 10·8. $C_{11}H_8O_6N_2$ requires N, 10·6%).

But-3-en-1-ol.—A mixture of but-3-yn-1-ol (249 g.), ethanol (1 l.), and 2·5% palladium–charcoal (20 g.) was shaken in hydrogen at room temperature and pressure. The absorption of hydrogen was regulated occasionally to allow the solution to cool, and was stopped when almost the theoretical quantity (*ca.* 80 l.) had been absorbed (6 hr.). From the filtered solution, most of the ethanol was distilled off through a Lessing column, and the residue was then fractionated through a 30 × 2 cm. Fenske column to give a main fraction (154 g.), b. p. 110—114°. Redistillation gave pure but-3-en-1-ol, b. p. 113—114°, n_D^{21} 1·4206. The 3 : 5-*dinitrobenzoate* formed pale yellow leaflets (from methanol), m. p. 45—47° (Found : C, 49·3; H, 3·8; N, 10·6. $C_{11}H_{10}O_6N_2$ requires C, 49·6; H, 3·8; N, 10·5%). The α-*naphthylurethane*, prepared in boiling ligroin (b. p. 100—120°), crystallised from light petroleum (b. p. 60—80°) in long needles, m. p. 78° (Found : C, 75·0; H, 6·5; N, 5·7. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3; N, 5·8%).

But-3-en-1-yl Bromide.—This was prepared by Linstead and Rydon's method (*J.*, 1934, 1995); redistillation of the fraction, b. p. 97—101°, gave the pure bromide (44 g., 66%), b. p. 99°, n_D^{22} 1·4625. Juvala (*Ber.*, 1930, **63**, 1989) recorded b. p. 98·5—99°, n_D^{20} 1·4621; Birch and McAllan (*J.*, 1951, 2556) give n_D^{20} 1·4575.

But-3-en-1-yl 2 : 3 : 4 : 6-*Tetra*-O-*acetyl*-β-D-*glucoside.*—A mixture of acetobromoglucose (82 g.), silver carbonate (35 g.), anhydrous sodium sulphate (25 g.), glass beads (50 g.) and dry benzene (150 c.c.) was vigorously stirred during the addition (15 min.) of but-3-en-1-ol (17·3 g.), and thereafter for 2 hr. at room temperature, 3 hr. at 60°, and 30 min. on the steam-bath under reflux. Salts were then filtered off, and the benzene was removed from the filtrate under reduced pressure to give a syrup, which partly crystallised at 0°. After trituration with ethanol (10 c.c.), the solid was collected and washed with ethanol–light petroleum (1 : 1); a second crop was obtained by the addition of the same mixed solvent to the mother-liquor. The *tetra*-O-*acetyl*-β-*glucoside* (23 g.) crystallised from this solvent in thick prisms, m. p. 80°, $[\alpha]_D^{20}$ −23·4° (*c*, 4·0 in $CHCl_3$) (Found : C, 53·8; H, 6·6. $C_{18}H_{26}O_{10}$ requires C, 53·7; H, 6·5%).

3 : 4-*Dibromobutyl* 2 : 3 : 4 : 6-*Tetra*-O-*acetyl*-β-D-*glucoside.*—To the butenyl tetra-acetyl-β-glucoside (13 g.) in carbon tetrachloride (150 c.c.), bromine (5·2 g.) in carbon tetrachloride (50 c.c.) was added during 2 hr.; the pale yellow solution was then evaporated under reduced

pressure and the residual oily *dibromide* (17·5 g.) finally dried at 50°/0·0001 mm. (Found: Br, 28·8. $C_{18}H_{26}O_{10}Br_2$ requires Br, 28·4%).

3 : 4-*Bisacetylthiobutyl* 2 : 3 : 4 : 6-*Tetra*-O-*acetyl*-β-D-*glucoside*.—The above dibromide (17·5 g.), potassium thiolacetate (8·2 g.), ethanol (110 c.c.), and thiolacetic acid (0·2 c.c.) were heated and stirred under reflux on the steam-bath under nitrogen for 6 hr. The solution was cooled, filtered from potassium bromide, concentrated to small volume, and then diluted with water (500 c.c.). Extraction with ether gave the *bisthiolacetate* (15·9 g.) as a viscous brown syrup, n_D^{19} 1·4962, $[\alpha]_D^{21}$ −17·2° (*c*, 3·0 in $CHCl_3$) (Found: C, 47·2; H, 6·0; S, 10·9; Ac, 44·2. $C_{28}H_{38}O_{13}S_2$ requires C, 47·8; H, 5·8; S, 11·6; Ac, 46·7%). Light absorption in ethanol: max. 2300 Å (ε 7500).

6-O-(*But*-3-*en*-1-*yl*)-1 : 2-3 : 4-*di*-O-iso*propylidene*-D-*mannitol*.—Sodium (1·2 g.), in small pieces, was added to but-3-en-1-ol (8 g.) heated on the steam-bath. When the reaction became slow, dry benzene (10 c.c.) was added, and the mixture was boiled under reflux until the metal had disappeared. A hot solution of 5 : 6-anhydro-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-mannitol (Bladon and Owen, *J.*, 1950, 591) (11·8 g.) in dry benzene (90 c.c.) was then added, and the boiling was continued for 7 hr. Water (200 c.c.) was added to the cooled reaction mixture, the benzene layer was removed, and the aqueous portion extracted once with benzene. The combined benzene solution was dried and evaporated to an oil, which on distillation gave the 6-*butenyl ether* (9·8 g., 64%) as a colourless oil, b. p. 130—140° (bath)/0·0001 mm., n_D^{19} 1·4580—1·4610. A fraction, n_D^{19} 1·4590, $[\alpha]_D^{23}$ +16° (*c*, 4 in EtOH), was analysed (Found: C, 60·5; H, 9·2. $C_{16}H_{28}O_6$ requires C, 60·75; H, 8·9%).

1-O-(*But*-3-*en*-1-*yl*)-D-*mannitol*.—A solution of the above *O*-butenyldi-*O*-*iso*propylidene-mannitol (8·8 g.) in ethanol (50 c.c.), water (50 c.c.), and sulphuric acid (2 g.) was boiled under reflux for 18 min., and then cooled, diluted with water (150 c.c.), neutralised with barium carbonate (30 g.), filtered, and evaporated to a syrup. This was dissolved in warm ethanol, filtered (charcoal), and again taken down to a syrup, which on dissolution in ethyl acetate deposited a solid (5·3 g.), m. p. 88—92°; recrystallisation from ethanol–ethyl acetate gave 1-O-(*but*-3-*en*-1-*yl*)-D-*mannitol*, m. p. 93—94°, $[\alpha]_D^{20}$ +7·3° (*c*, 3 in H_2O) (Found: C, 50·7; H, 8·7. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·5%).

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(*but*-3-*en*-1-*yl*)-D-*mannitol*.—Acetylation of the 1-*O*-butenylmannitol (12·3 g.) with acetic anhydride (100 c.c.) and fused sodium acetate (6 g.) at 100° for 6 hr. gave the *penta-acetate*, which crystallised from aqueous ethanol in small prisms, m. p. 61—63°, $[\alpha]_D^{21}$ +29·4° (*c*, 7 in EtOH) (Found: C, 53·8; H, 6·9. $C_{20}H_{30}O_{11}$ requires C, 53·8; H, 6·8%).

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(3 : 4-*dibromobutyl*)-D-*mannitol*.—Bromine (7·5 g.) in carbon tetrachloride (70 c.c.) was slowly added (30 min.) to a stirred solution of the above penta-acetate (20 g.) in carbon tetrachloride (130 c.c.), and after a further 30 min. the solution was washed with aqueous sodium sulphite, dried, and evaporated to a syrup (25·5 g.), n_D^{20} 1·4767. This was dissolved in ethanol (40 c.c.), and water was added to slight turbidity; cooling overnight then gave a solid (12 g.), which after 6 recrystallisations from ethanol–light petroleum formed colourless prisms of the *dibromide*, m. p. 87°, $[\alpha]_D^{21}$ +42·2° (*c*, 5 in $CHCl_3$) (Found: C, 39·5; H, 5·3; Br, 26·2. $C_{20}H_{30}O_{11}Br_2$ requires C, 39·6; H, 5·0; Br, 26·4%).

The syrup obtained by evaporation of all mother-liquors was fractionally distilled at 190—220° (bath)/0·0004 mm. to give: (*a*) 2·4 g., n_D^{21} 1·4660; (*b*) 6·6 g., n_D^{21} 1·4741; (*c*) 3·0 g., n_D^{21} 1·4780; (*d*) 0·8 g., n_D^{21} 1·4800. The purity of (*b*), (*c*), and (*d*), from determinations of their bromine content, was 84, 95, and 93% respectively, but no more crystalline dibromide could readily be isolated from them, probably because of the presence of the other stereoisomer. Fraction (*a*) partly crystallised, and the solid material, after several recrystallisations from ethanol–light petroleum and from benzene–light petroleum, was identified as hexa-*O*-acetyl-D-mannitol, m. p. and mixed m. p. 122—124°, $[\alpha]_D^{20}$ +25° (*c*, 1 in $CHCl_3$) (Found: C, 49·8; H, 6·2. Calc. for $C_{18}H_{26}O_{12}$: C, 49·8; H, 6·0%).

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(3 : 4-*bisacetylthiobutyl*)-D-*mannitol*.—The crystalline dibromide (5 g.), potassium thiolacetate (2·4 g.), and ethanol (50 c.c.) were boiled together under nitrogen for 6 hr., and the product was isolated as described for the glucoside. The *bisthiolacetate* was a pale yellow syrup, n_D^{22} 1·4883, $[\alpha]_D^{22}$ +9·2° (*c*, 6 in $CHCl_3$) (Found: C, 48·2; H, 6·3; S, 10·3. $C_{34}H_{46}O_{13}S_2$ requires C, 48·3; H, 6·1; S, 10·7%). It could be distilled in small quantities at 240—250° (bath)/0·0001 mm., without change in refractive index. Light absorption: max. 2300 Å (ε 7600).

6-O-(*But*-3-*en*-1-*yl*)-1 : 3-2 : 4-*di*-O-*ethylidene*-D-*glucitol*.—To a hot solution of sodium (4·7 g.) in but-3-en-1-ol (40 g.), a solution of 5 : 6-anhydro-1 : 3-2 : 4-di-*O*-ethylidene-D-glucitol (41 g.)

(Bladon and Owen, *J.*, 1950, 591) in dry benzene (250 c.c.) was added. The mixture was boiled under reflux for 7 hr., then diluted with water (200 c.c.) and partly neutralised with acetic acid (10 g.). The benzene layer was removed, and the aqueous portion extracted with benzene (4 × 150 c.c.); evaporation of the dried benzene solutions then gave an oil, which on fractional distillation furnished the **6-*butenyl ether*** (32 g., 59%) as a viscous syrup, b. p. 165—175° (bath)/0·0004 mm., n_D^{20} 1·4790, $[\alpha]_D^{20}$ +4·8° (*c*, 4·1 in $CHCl_3$) (Found: C, 57·7; H, 8·7. $C_{14}H_{24}O_6$ requires C, 58·3; H, 8·4%).

The highest-boiling fraction partly crystallised, and recrystallisation of the solid first from benzene–light petroleum and then from ethanol–light petroleum gave prisms, m. p. 158°, of (probably) 6-O-(*but*-3-*en*-1-*yl*)-1 : 3·2 : 4-*di*-O-*ethylidene*-D-*glucitol*-5 1 : 3·2 : 4-*di*-O-*ethylidene*-D-*glucitol*-6 *ether* (IX) (Found: C, 57·6, 57·1; H, 8·2, 8·3. $C_{24}H_{40}O_{11}$ requires C, 57·1; H, 8·0%). The substance was unsaturated, and on microhydrogenation absorbed 0·8 mol. of hydrogen. It was readily soluble in benzene, but sparingly so in cold methanol, ethanol, and carbon tetrachloride. (The foregoing name is used non-commitally pending Anglo-U.S. or I.U.P.A.C. recommendations for this type of compound.)

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(*but*-3-*en*-1-*yl*)-D-*glucitol*.—The 6-*O*-butenyldi-*O*-ethylideneglucitol (29 g.) was heated on the steam-bath for 3·5 hr. with 4% aqueous sulphuric acid (300 c.c.) and ethanol (150 c.c.). The cooled solution was extracted once with benzene to remove oily impurities, and then neutralised with barium carbonate, filtered, and evaporated to a syrup (22 g.). This crude 6-*O*-(but-3-en-1-yl)-D-glucitol (21 g.) was heated at 100° for 10 hr. with acetic anhydride (120 c.c.) and fused sodium acetate (12 g.); the solution was then concentrated under reduced pressure and the residue was stirred with water. Extraction with chloroform gave a brown oil, which on distillation furnished the colourless *penta-acetate* (26 g.), b. p. 190—210° (bath)/0·001 mm., n_D^{21} 1·4545, $[\alpha]_D^{22}$ +4·9° (*c*, 5 in $CHCl_3$) (Found: C, 54·2; H, 7·0. $C_{20}H_{30}O_{11}$ requires C, 53·8; H, 6·8%).

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(3 : 4-*dibromobutyl*)-D-*glucitol*.—Addition of bromine (8·8 g.) in carbon tetrachloride (100 c.c.) to the above penta-acetate (23·5 g.) in carbon tetrachloride (150 c.c.) gave, on distillation of the product, the *dibromide* (21·1 g.), b. p. 210—240° (bath)/0·001 mm., n_D^{20} 1·4842—1·4865. A fraction, n_D^{20} 1·4860, $[\alpha]_D^{18}$ −3·7° (*c*, 5 in $CHCl_3$), was analysed (Found: C, 39·8; H, 5·3; Br, 26·7. $C_{20}H_{30}O_{11}Br_2$ requires C, 39·6; H, 5·0; Br, 26·4%).

1 : 2 : 3 : 4 : 5-*Penta*-O-*acetyl*-6-O-(3 : 4-*bisacetylthiobutyl*)-D-*glucitol*.—The above dibromide (12·9 g.), potassium thiolacetate (6 g.), ethanol (120 c.c.) and thiolacetic acid (0·2 g.) were boiled together under nitrogen for 6 hr., and the mixture was then worked up as already described for the glucoside. The crude bisthiolacetate was a dark red viscous syrup (10 g.), n_D^{20} 1·5027, which had undergone slight deacetylation (Found: C, 46·7; H, 6·1; S, 11·3; Ac, 46·6. Calc. for $C_{24}H_{36}O_{12}S_2$: C, 48·3; H, 6·1; S, 10·7; Ac, 50·5%). Light absorption in ethanol: max. 2290 Å (ε 6000).

3-O-(*But*-3-*en*-1-*yl*)-1 : 2·5 : 6-*di*-O-iso*propylidene*-D-*mannitol*.—A hot solution of sodium hydroxide (70 g.) in water (70 c.c.) was gradually added to a vigorously stirred solution of 1 : 2·5 : 6-di-*O*-*iso*propylidene-D-mannitol (55·5 g.) (Baer, *J. Amer. Chem. Soc.*, 1945, **67**, 338) in dioxan (200 c.c.) heated on the steam-bath under reflux. Stirring and heating of the emulsion were maintained for 20 hr., but-3-en-1-yl bromide (18·5 g.) in dioxan (35 c.c.) being added dropwise during the first 4 hr., and more bromide (18·5 g.) in dioxan (25 c.c.) between the 8th and the 12th hour. After completion of the reaction, the mixture was concentrated under reduced pressure to remove dioxan, and then treated with ice (200 g.) and partly neutralised with 20% aqueous sulphuric acid (300 c.c.). Extraction with ether (7 × 200 c.c.), and evaporation of the dried extracts gave an oil, which was dissolved in warm light petroleum (b. p. 60—80°) (250 c.c.) and cooled to 0°; unchanged di*iso*propylidenemannitol (21 g.) crystallised, and was removed, a further crop (2 g.) being obtained on concentration of the filtrate. Evaporation of the residual solution, and distillation of the residue, gave the 3-(*but*-3-*en*-1-*yl*) *ether* (33·3 g., 85% based on di*iso*propylidene compound consumed) as a viscous oil, b. p. 135—145° (bath)/0·0004 mm., n_D^{20} 1·4585, $[\alpha]_D^{21}$ +10·7° (*c*, 3 in EtOH) (Found: C, 60·6; H, 9·2. $C_{16}H_{28}O_6$ requires C, 60·7; H, 8·9%).

Conditions for this reaction are apparently critical, and repetitions of the above experiment gave much poorer yields. Variations in the concentration of alkali, method and time of addition of butenyl bromide, shape and position of stirrer, and the addition of surface-active agents failed to give satisfactory results. A low yield of the butenyl ether was obtained by interaction of the monosodium derivative of 1 : 2·5 : 6-di-*O*-*iso*propylidenemannitol (prepared by evaporation of a solution of the di*iso*propylidenemannitol and 1 atomic proportion of sodium in liquid ammonia) with excess of butenyl bromide in boiling dioxan.

3-O-(*But-3-en-1-yl*)-D-*mannitol*.—The above butenyl ether (7·7 g.), ethanol (40 c.c.), water (40 c.c.), and sulphuric acid (2 g.) were boiled together under reflux on the steam-bath for 15 min., then rapidly cooled, diluted with water (100 c.c.), and stirred with barium carbonate (25 g.). The neutral solution was filtered and evaporated to a syrup, which was dissolved in ethanol (50 c.c.), shaken with a little charcoal, filtered, and again concentrated; the product was dissolved in ethyl acetate (50 c.c.) and stored at 0° overnight. The crystals so formed were collected (4·7 g.; m. p. 91—93°), and recrystallised from ethanol–ethyl acetate to give prisms of 3-O-(*but-3-en-1-yl*)-D-*mannitol*, m. p. 93—96°, $[\alpha]_D^{22}$ +16·7° (*c*, 4 in H_2O) (Found: C, 50·4; H, 8·8. $C_{10}H_{20}O_6$ requires C, 50·8; H, 8·5%).

1 : 2 : 4 : 5 : 6-*Penta*-O-*acetyl*-3-O-(*but-3-en-1-yl*)-D-*mannitol*.—Acetylation of the preceding butenyl ether (1·8 g.) with acetic anhydride (20 c.c.) and fused sodium acetate (1 g.) for 7 hr. at 100° gave an oil, which on distillation furnished the *penta-acetate* (2·8 g.), b. p. 190—215° (bath)/0·0001 mm., n_D^{16} 1·4534, $[\alpha]_D^{17}$ +32·3° (*c*, 5 in $CHCl_3$) (Found: C, 53·3; H, 7·0. $C_{20}H_{30}O_{11}$ requires C, 53·8; H, 6·8%); this contained a small proportion of hexa-*O*-acetylmannitol (see below).

1 : 2 : 4 : 5 : 6-*Penta*-O-*acetyl*-3-O-(3 : 4-*dibromobutyl*)-D-*mannitol*.—The above penta-acetate (2·5 g.) in carbon tetrachloride (30 c.c.) was gradually treated with bromine (1 g.) in carbon tetrachloride (15 c.c.). The reaction appeared to cease after about three-quarters of the bromine solution was added, and after being set aside overnight the mixture was still deeply coloured; it was therefore washed successively with aqueous sodium hydrogen sulphite, aqueous sodium hydrogen carbonate, and water, and finally dried and evaporated to an oil (2·6 g.). This was distilled from a small retort, the following fractions being collected at 215—235° (bath)/0·0004 mm.: (*a*) 0·8 g., n_D^{19} 1·4600; (*b*) 0·5 g., n_D^{19} 1·4673; (*c*) 0·8 g., n_D^{19} 1·4793; (*d*) 0·4 g., n_D^{19} 1·4833. The first two fractions were cloudy, and when (*a*) was treated with ethanol–light petroleum (b. p. 60—80°) it gave hexa-*O*-acetylmannitol, m. p. and mixed m. p. 124°. Fraction (*d*) was the required *dibromide* (Found: C, 40·0; H, 5·3; Br, 26·9. $C_{20}H_{30}O_{11}Br_2$ requires C, 39·6; H, 5·0; Br, 26·4%).

Deacetylation of Thiolacetates.—(i) To a stirred solution of 3 : 4-bisacetylthiobutyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (9·3 g.) in dry methanol (100 c.c.), kept at about −17°, under nitrogen, 1·5N-methanolic barium methoxide (40 c.c.) was added. The temperature was allowed to rise to 0° (2 hr.) (the barium salt began to separate after 25 min.) and the mixture was then warmed to 25° for 15 min., stirring being maintained throughout; a further quantity of barium salt was suddenly precipitated at the higher temperature. The solid was filtered off under nitrogen, and was washed with dry methanol and with dry ether, and dried in a vacuum over phosphoric oxide. The barium salt (5·1 g.) was a fine yellow hygroscopic powder, $[\alpha]_D^{22}$ −16° (*c*, 4 in 1% aqueous HCl) (Found: C, 24·8; H, 4·6; S, 11·7; thiol-S, 9·25; Ba, 29·9. Calc. for $C_{16}H_{16}O_6S_2Ba$: C, 27·6; H, 4·2; S, 14·7; Ba, 31·5%).

(ii) (With P. S. Fitt.) Similar treatment of crystalline 2 : 3-bisacetylthiopropyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (Evans and Owen, *loc. cit.*) gave the barium salt of 2 : 3-dimercaptopropyl β-D-glucoside (Found: C, 26·7; H, 3·7; S, 13·25; thiol-S, 11·7; Ba, 27·9. Calc. for $C_9H_{16}O_6S_2Ba$: C, 25·6; H, 3·8; S, 15·2; Ba, 32·6%).

(iii) Similar treatment of penta-*O*-acetyl-6-*O*-(3 : 4-bisacetylthiobutyl)-D-mannitol gave a barium salt, $[\alpha]_D^{18}$ −7·7° (*c*, 4 in 2N-HCl) (Found: C, 29·3; H, 6·1; S, 12·1; thiol-S, 10·8; Ba, 27·3. Calc. for $C_{16}H_{30}O_8S_2Ba$: C, 27·4; H, 4·6; S, 14·6; Ba, 31·4%).

The same hepta-acetyl compound (0·97 g.) was boiled under reflux with methanol (30 c.c.) and concentrated hydrochloric acid (3 c.c.) for 2 hr. in nitrogen. The solution was then concentrated under reduced pressure, and the residue repeatedly evaporated under reduced pressure with dry methanol (4 × 10 c.c.) to give a yellow glass (Found: C, 37·0; H, 7·7; S, 17·1; thiol-S, 8·4%). This was dissolved in warm ethanol (1·5 c.c.) and cooled to 0° to give a colourless solid (0·2 g.), which was readily soluble in water; it sintered at 57—60° and became waxy at 85—95° (Found: C, 41·1; H, 7·1; S, 23·9; thiol-S, 11·2. Calc. for $C_{16}H_{30}O_6S_2$: C, 42·3; H, 7·1; S, 22·6; thiol-S, 11·3%).

(iv) Penta-*O*-acetyl-6-*O*-(3 : 4-bisacetylthiobutyl)-D-glucitol with methanolic barium methoxide gave a salt of poor quality (Found: C, 33·7; H, 6·1; S, 15·2; thiol-S, 7·1; Ba, 19·5. Calc. for $C_{16}H_{30}O_8S_2Ba$: C, 27·4; H, 4·6; S, 14·6; Ba, 31·4%).

Fission of Butenyl Ethers of Mannitol with Aqueous Acid.—(A) *Formation of mannitol*. (i) 3-*O*-(But-3-en-1-yl)-1 : 2-5 : 6-di-*O*-*iso*propylidene-D-mannitol (35 g.) was heated on the steam-bath with N-sulphuric acid (125 c.c.) for 3·5 hr. (the mixture became homogeneous after 20 min.). The cooled solution was neutralised with barium carbonate, filtered, and evaporated to a semi-solid residue (22 g.), which was dissolved in hot water (20 c.c.) and ethanol (150 c.c.),

and cooled to 0° to give mannitol (11·5 g.), m. p. and mixed m. p. 166°. Evaporation of the filtrate gave material which on fractional crystallisation from 90% ethanol and from ethanol–ether gave more mannitol (1·4 g.) and crude 3-*O*-butenylmannitol (4 g.), m. p. 82—86°, raised after several recrystallisations from ethanol–ethyl acetate to m. p. and mixed m. p. 93—96°.

(ii) 3-*O*-(But-3-en-1-yl)-D-mannitol (0·5 g.) was boiled under reflux with water (10 c.c.) and sulphuric acid (1 g.). The reaction, followed polarimetrically, was complete in 1 hr.: $[\alpha]_D^{20}$ (initial) +16·5°, (final) +4°. After 3 hr. the solution was neutralised with barium carbonate and worked up as described above to give mannitol (0·1 g.), m. p. and mixed m. p. 166°.

(B) *Volatile products.* (i) 3-*O*-Butenylmannitol (2 g.) and 2N-sulphuric acid (20 c.c.) were boiled under reflux for 70 min. The cooled solution was neutralised with sodium carbonate and continuously extracted with ether for several hours. The dried (K_2CO_3) extract was fractionated to remove ether, and the residue on distillation gave 80 mg., boiling up to 135° (bath), which were unsaturated and gave a strong iodoform reaction; this product gave a 3 : 5-dinitrobenzoate, m. p. 29—39°, insufficient for purification. The 3 : 5-*dinitrobenzoate* of authentic but-1-en-3-ol, prepared in pyridine, crystallised from methanol in soft flattened needles, m. p. 58° (Found: N, 10·7. $C_{11}H_{10}O_6N_2$ requires N, 10·5%).

(ii) The above experiment was repeated, a slow stream of nitrogen being passed through the reaction mixture and then *via* a drying tube ($CaCl_2$) into a solution of bromine in carbon tetrachloride. Concentration of the latter solution gave an oil which on trituration with cold ethanol furnished butadiene tetrabromide, m. p. and mixed m. p. 115—118° (sealed tube). No tetrabromide was obtained when mannitol (1 g.), but-3-en-1-ol (0·4 g.), and 2N-sulphuric acid (10 c.c.) were similarly treated.

(iii) 6-*O*-(But-3-en-1-yl)-1 : 2-3 : 4-di-*O*-*iso*propylidene-D-mannitol (5 g.) was heated on the steam-bath for 3 hr. with N-sulphuric acid (50 c.c.), in a stream of nitrogen; the butadiene in the exit gases was detected colorimetrically with diazotised 2 : 4-dinitroaniline (Terent'ev and Demidova, *Chem. Abs.*, 1943, **37**, 2682) and with alkaline methanolic sodium nitroprusside (cf. Scagliarini and Lucchi, *ibid.*, 1940, **34**, 2287). Fractional crystallisation of the product isolated from the reaction solution gave mannitol (0·5 g.), m. p. and mixed m. p. 163—166°, and 6-*O*-butenylmannitol (1·25 g.), m. p. and mixed m. p. 91—93°.

Rates of Hydrolysis of Glucosides.—A solution of allyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (0·194 g.) in methanolic sodium methoxide (from 20 mg. of sodium in 10 c.c. of methanol) was boiled under reflux for 15 min. and then evaporated to dryness under reduced pressure. The residual allyl β-D-glucoside was dissolved in 0·28N-sulphuric acid (10 c.c.), and the filtered solution was heated on the steam-bath, the hydrolysis being followed polarimetrically. A similar experiment was carried out with an equivalent quantity (0·201 g.) of but-3-en-1-yl tetra-*O*-acetyl-β-D-glucoside. The following values of α_D^{20} (1-dm. tube) were observed:

Time (hr.)	0	0·5	3	8	14	36
Allyl glucoside	−0·44°	−0·40°	−0·25°	+0·01°	+0·24°	+0·46° (const.)
Butenyl ,, ...	−0·38°	−0·34°	−0·22°	+0·02°	+0·23°	+0·45° (const.)

The half-life for each glucoside is *ca.* 8·5 hr. The initial values correspond to $[\alpha]_D^{20}$ −40° and −33° for the two glucosides respectively; Fischer (*Z. physiol. Chem.*, 1920, **108**, 3) gives $[\alpha]_D^{17}$ −40·5° for allyl β-D-glucoside in water. The final constant rotations, calculated for glucose, correspond to $[\alpha]_D^{20}$ +51° and +50° respectively; the equilibrium value for D-glucose is +52·7° in water.

In this and the following paper, absorption spectra were determined by Mrs. A. I. Boston, and microanalyses were by Mr. F. H. Oliver and his staff (Organic Micro-Analytical Laboratory). Grateful acknowledgment is made to the Medical Research Council for a grant to purchase special chemicals, and to the Government of Madhya Bharat, India, for the award of a Foreign Scholarship (to N. S. J.).

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Dithiols. Part XVI. The O-β-D-Glucoside of 1 : 3-Dimercaptopropan-2-ol.*

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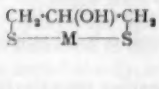
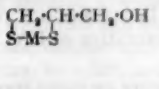
The hexa-acetyl derivative of the above glucoside has been synthesised from 1 : 3-dihydroxyprop-2-yl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside, which is conveniently prepared by selective acid hydrolysis of its *O*-benzylidene compound. Deacetylation of the hexa-acetyl derivative gives the dithiol (isolated as the barium salt); an anhydro-compound has also been obtained.

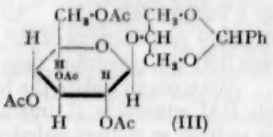
Although 1 : 3-dimercaptopropan-2-ol is more toxic than 2 : 3-dimercaptopropanol (BAL), it is reported to be more effective than the latter in reversal of succinoxidase inhibition caused by cadmium, mercury, and bismuth poisoning (Barron and Kalnitsky, *Biochem. J.*, 1947, **41**, 346); possibly the six-membered metal-containing ring (I) is more stable for those elements than the five-membered structure (II) derived from BAL. The toxicity of BAL is considerably reduced when it is administered in the form of its *O*-glucoside (Danielli, Danielli, Mitchell, Fraser, Owen, and Shaw, *ibid.*, p. 325), and the same would be expected to apply to the analogous derivative of 1 : 3-dimercaptopropan-2-ol.



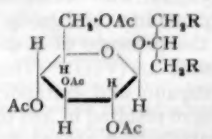
(I)



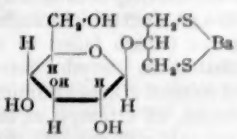
(II)



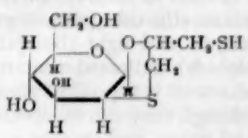
(III)



(IV; R = OH) * (VI; R = SAc)
(V; R = O·SO$_2$·C$_6$H$_4$Me-*p*)



(VII)



(VIII)

Formation of the glucoside by reaction of the 1 : 3-dithiol with glucose or with acetobromoglucose is not feasible because reaction would occur preferentially with the thiol rather than the hydroxy-group. A synthesis must therefore involve either protection of the dithiol (*e.g.*, as the *SS'*-benzylidene derivative) before reaction with the sugar, or the introduction of the thiol groups after the *O*-glucosidic linkage has been formed. The latter approach appeared the more promising and an attempt was made to convert 1 : 3-dibromopropan-2-ol into its glucoside, with the object of eventual replacement of halogen by thiol. However, reaction of the dibromohydrin with acetobromoglucose in the presence of silver carbonate gave a bromine-free product, and investigation showed that the dibromohydrin itself was rapidly debrominated by silver carbonate alone. A less direct method was therefore necessary.

Carter (*Ber.*, 1930, **63**, 1684) has described the small-scale preparation of 1 : 3-dihydroxyprop-2-yl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (IV) by catalytic hydrogenation of the 1 : 3-benzylidene compound (III), obtained by condensation of acetobromoglucose with 1 : 3-*O*-benzylideneglycerol. The preparation of the benzylideneglycerol is tedious, because of the low yield of the 1 : 3-isomer which has to be separated from the considerable proportion of 1 : 2-compound also formed (cf. Evans and Owen, *J.*, 1949, **244**; and references there cited), but it has now been found (by development of some preliminary observations by Mr. M. E. Baguley of this Department) that perchloric acid is an effective catalyst not

* Part XV, preceding paper.

only for the initial condensation of benzaldehyde with glycerol but also for the partial isomerisation of the unwanted 1 : 2- into the 1 : 3-compound; a 40% yield of recrystallised 1 : 3-*O*-benzylideneglycerol was thus obtained. Conversion into the 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside proceeded smoothly, but removal of the benzylidene group by Carter's method was impracticable on a large scale owing to the considerable quantity of catalyst required (Carter used palladium black in amount almost equal to that of the benzylidene compound). Pilot experiments showed that the benzylidene group was considerably more sensitive towards acid hydrolysis than either the glycosidic linkage or the acetyl groups, and conditions were devised under which 10—20-g. quantities of the glucoside (IV) could be prepared in *ca.* 80% yield by controlled hydrolysis in aqueous-alcoholic sulphuric acid. Introduction of the thiol groups followed Chapman and Owen's general method (*J.*, 1950, 579), (IV) being converted into its crystalline ditoluene-*p*-sulphonate (V), which with potassium thiolacetate gave the pure hexa-acetyl derivative (VI) of the glucoside.

Deacetylation with methanolic barium methoxide, as previously carried out on many acetylated polyhydroxy-dithiols, was not applicable in the present instance because of the low solubility of the hexa-acetate (VI) in the reagent, but when the compound was treated with ethanolic sodium ethoxide it rapidly dissolved, and the thiol value of the solution attained over 90% of the theoretical value, indicating that deacetylation had largely followed a normal course, and was accompanied by only a small amount of cyclisation or other side-reactions. Addition of methanolic barium methoxide then precipitated the dithiol as a barium salt (VII). Although the latter was not pure, its quality was similar to that of many preparations of the isomeric derivative of BAL; the ratio of thiol to total sulphur was 0·81 (cf. preceding paper).

Attempts to isolate the free dithiol were no more successful than the earlier experiments on BAL-glucoside (Danielli *et al.*, *loc. cit.*; and unpublished observations). Removal of sodium as sodium chloride, from the solution obtained by deacetylation with ethanolic sodium ethoxide, gave on evaporation a product which contained only one free thiol group; analysis and light-absorption properties (which failed to indicate the presence of a disulphide) indicated that it was probably an anhydro-derivative, such as (VIII). This behaviour is typical of glucosides and hexitol ethers of dimercapto-propanol and -butanol; although they can be obtained in solution, all attempts at isolation have resulted in loss of thiol value, and storage as the barium salt still remains the most satisfactory procedure. The only instance in which the pure dithiol has been isolated from its barium salt was with the tetramethyl ether of BAL-glucoside (Miles and Owen, *J.*, 1950, 2934), in which cyclisation cannot occur.

Experimental

1 : 3-O-*Benzylideneglycerol.*—A mixture of benzaldehyde (253 g.), glycerol (216 g.), and 60% perchloric acid (2·5 c.c.), heated (water-bath at 80—90°) in a stream of nitrogen, at 60—70 mm., became clear in 40 min., and after a further 10 min. it was cooled, diluted with ether (400 c.c.), and washed with 1% aqueous potassium carbonate (2 × 500 c.c.). The dried (K_2CO_3) ethereal solution was evaporated to an oil (325 g.) which was dissolved in warm benzene (300 c.c.), diluted with petroleum (400 c.c.; b. p. 80—100°), decanted from a small amount of oil, and cooled to −10° to give the 1 : 3-benzylidene derivative (67 g.), m. p. 64—68°. Dilution of the mother-liquors with more petroleum gave a heavy oil, which was removed and mixed with perchloric acid (0·5 c.c.); this partly crystallised at 0°, and filtration afforded a further 82 g. of crude 1 : 3-benzylidene derivative, m. p. 47—55°. By re-treatment of the oily filtrate with more perchloric acid the total yield of crude solid derivatives was raised to 180 g. Recrystallisation from benzene–light petroleum (3 : 4) gave 74 g., m. p. 65—67°, and 65 g., m. p. 60—65° (the mixture of stereoisomers usually obtained has a m. p. in the range 60—70°).

During recrystallisation of the crude material the temperature should not be above 50°, and the warm solution should be chilled rapidly; otherwise, the presence of traces of perchloric acid catalyses the re-establishment of the 1 : 2 ⇌ 1 : 3 equilibrium, with consequent heavy loss of the 1 : 3-isomer.

2-O-(2 : 3 : 4 : 6-*Tetra*-O-*acetyl*-β-D-*glucosyl*)*glycerol.*—A suspension of 1 : 3-*O*-benzylidene-2-*O*-(2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucosyl)glycerol (29 g.) (Carter, *Ber.*, 1930, **63**, 1684) in

ethanol (120 c.c.) at 50° was vigorously stirred during the rapid addition of N-sulphuric acid (120 c.c.) (preheated to 50°) and for a further 7 min. (the mixture became homogeneous in 2 min.). The solution was then quickly cooled to 0° (3 min.) and maintained at 0° whilst being neutralised with barium carbonate (40 min.). Barium salts were then filtered off and washed with hot ethanol, and the filtrate and washings were evaporated to a syrup, which was dried by azeotropic evaporation with benzene–ethanol. It was then dissolved in hot benzene (50 c.c.), filtered, and diluted with ether (25 c.c.); the cooled solution deposited a solid (17·5 g.) which on recrystallisation from benzene–ether gave the 2-*O*-(tetra-acetyl-β-glucosyl)glycerol as needles, m. p. 101—102°, $[\alpha]_D^{20}$ −22° (*c*, 5 in H_2O). Carter (*loc. cit.*) gives m. p. 103° (corr.), $[\alpha]_D^{19}$ −22·1° (in H_2O).

Ditoluene-p-*sulphonate*. A solution of the above compound (14 g.) with toluene-*p*-sulphonyl chloride (12·5 g.) in pyridine (140 c.c.) was kept at 0° overnight. Water (5 c.c.) was then added, and most of the pyridine was removed under reduced pressure. The residue was worked up with chloroform in the usual way and gave an oil, which was dissolved in hot methanol (40 c.c.) and light petroleum (b. p. 60—80°) (10 c.c.); after storage in the refrigerator the *derivative* (17·5 g.) crystallised. Recrystallisation from methanol gave prisms, m. p. 107—109°, $[\alpha]_D^{20}$ +1·5° (*c*, 4 in $CHCl_3$) (Found: C, 50·7; H, 5·4; S, 8·7. $C_{31}H_{38}O_{16}S_2$ requires C, 50·9; H, 5·2; S, 8·8%).

1 : 3-*Bisacetylthioprop*-2-*yl* 2 : 3 : 4 : 6-*Tetra*-*O*-*acetyl*-β-D-*glucoside*.—A solution of the ditoluene-*p*-sulphonate (12 g.) and potassium thiolacetate (4·7 g.) in ethanol (150 c.c.) was stirred and boiled for an hour under reflux in a slow stream of nitrogen. The precipitated potassium toluene-*p*-sulphonate was filtered off and washed with hot ethanol, and the filtrate and washings were evaporated under reduced pressure. The residue was treated with water and chloroform, and the organic layer was dried and evaporated to give a gelatinous solid, which was dissolved in hot ethanol (50 c.c.) and diluted with light petroleum (100 c.c.). The solution was cooled slowly, with constant stirring, to −20°, and the gelatinous precipitate was collected and washed with ethanol–light petroleum (1 : 3); it retained a considerable amount of solvent which was removed at 10^{-4} mm. to give the *bisthiolacetate* as a microcrystalline solid, m. p. 98—102°, $[\alpha]_D^{19}$ +13·3° (*c*, 6 in $CHCl_3$) (Found: C, 47·0; H, 5·6; S, 11·7; Ac, 48·4. $C_{31}H_{50}O_{12}S_2$ requires C, 46·8; H, 5·6; S, 11·9; Ac, 48·0%). Light absorption in ethanol: max. 2280 Å (ε 8300).

Deacetylation. Quantitative tests showed that when the above compound was treated, under nitrogen, with excess of methanolic sodium methoxide at 20°, over 90% of the theoretical thiol value was attained in 30 min., as estimated by acidification and titration with iodine. The following preparative experiments were carried out:

(i) The hexa-acetyl compound (1·1 g.) was stirred at 0°, under nitrogen, with 0·3N-methanolic sodium methoxide (20 c.c.). When the mixture became homogeneous (30 min.), 1·2N-methanolic barium methoxide (5 c.c.) was added. The clear solution was warmed to 35°, the barium salt of the dithiol being suddenly precipitated. It was collected by centrifugation, and washed successively with dry methanol, dry ethanol, dry ether, and then dried in a vacuum over phosphoric oxide; it formed a fine white powder (0·8 g.) (Found: C, 22·2; H, 4·2; S, 11·8; thiol-S, 9·6; Ba, 39·2. Calc. for $C_8H_{16}O_6S_2Ba$: C, 25·6; H, 3·8; S, 15·2; Ba, 32·6%). The analysis indicated that it contained other adsorbed barium salts, but the thiol-S/total-S ratio, 0·81, was satisfactory.

(ii) The hexa-acetyl compound (1·9 g.) was shaken at 0° under nitrogen with ethanolic sodium ethoxide, from sodium (0·3 g.) and ethanol (20 c.c.). The solution (the thiol value of which had attained 91% of the theoretical for complete deacetylation) was then treated with 99% of the theoretical quantity (based on total sodium) of ethanolic hydrogen chloride, and the precipitated sodium chloride was filtered off. The filtrate was evaporated to a syrup which was dissolved in dioxan (15 c.c.), filtered, and freeze-dried in a high vacuum, to give a very hygroscopic, colourless glass (0·95 g.), probably the *anhydro*-derivative of the dimercaptopropylglucoside (Found: C, 40·0; H, 6·65; thiol-S, 12·8. $C_8H_{16}O_5S_2$ requires C, 40·3; H, 6·0; thiol-S, 12·0%). Light absorption in ethanol: infl. *ca.* 2250 Å (ε 400). Although initially readily soluble in ethanol, it became insoluble after storage for a few weeks.

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Dithiols. Part XVII. S-Benzyl Derivatives of 2 : 3-Dimercaptopropanol and 1 : 3-Dimercaptopropan-2-ol.*

By N. S. Johary and L. N. Owen.

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Reaction of 2 : 3-dibromopropanol or its acetate with the sodium derivative of toluene-ω-thiol results in rearrangement; the product is 1 : 3-bisbenzylthiopropan-2-ol, which is also obtained by selective benzylation of 1 : 3-dimercaptopropan-2-ol. 2 : 3-Bisbenzylthiopropanol is similarly prepared from 2 : 3-dimercaptopropanol, and the structures of both bisbenzyl compounds are established by reduction to the dimercapto-alcohols and desulphurisation of the latter. The infrared absorption spectra of 1 : 3-bisbenzylsulphinylpropan-2-ol and of 1 : 3-bisbenzylsulphonylpropan-2-ol are discussed. The synthesis of 2 : 3-bisbenzylthiopropyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside is described.

Difficulties which arise in the isolation of polyhydroxy-derivatives of 2 : 3-dimercaptopropanol (BAL) (I) and of other dithiols have been attributed to the occurrence of side-reactions, probably involving cyclisation, during deacetylation of the fully-acetylated compounds (Harding and Owen, *J.*, 1954, 1536). If the thiol groups were protected in some other way than as acetylthio-functions, such that removal of *O*-acetyl groups could precede the regeneration of free thiol, then cyclisation (which involves attack by $-SH$ on $>C-OAc$) should be avoided. The present paper describes some exploratory experiments involving protection by benzyl groups, and eventual regeneration of the free thiol by hydrogenolysis (cf. "Organic Reactions," Vol. VII, p. 263). For the present investigation, 2 : 3-bisbenzylthiopropanol (II) was chosen as a model substance; Stocken (*J.*, 1947, 592) mentioned that BAL could be regenerated from it by treatment with sodium in liquid ammonia, but no details were given.

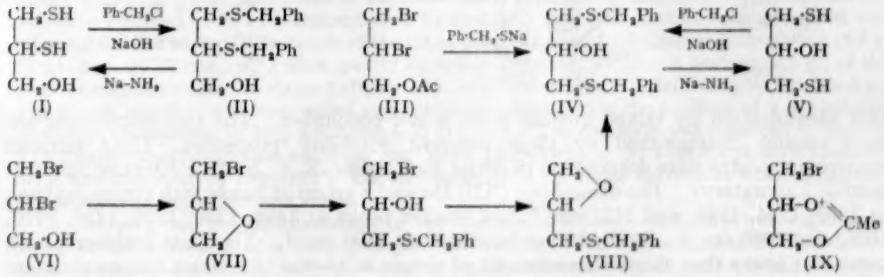
Kostir and Kral (*Coll. Czech. Chem. Comm.*, 1949, **14**, 219) attempted the preparation of the acetate of (II) by reaction of 2 : 3-dibromopropyl acetate (III) with the sodium derivative of toluene-ω-thiol, but they obtained only an impure product which decomposed with the formation of stilbene when distilled at 0·5 mm.; the stilbene was presumably formed from dibenzyl disulphide, which is known to yield the hydrocarbon when strongly heated (Fromm and Achert, *Ber.*, 1903, **36**, 534). In our hands the replacement reaction occurred very readily in ethanol, and the product distilled at low pressure without decomposition, no stilbene being encountered; the material, however, was found to be largely deacetylated, solvolysis presumably having occurred under the basic conditions of the experiment. Deacetylation was therefore completed catalytically with ethanolic sodium ethoxide, and the resulting analytically pure bisbenzylthiopropanol was characterised as the crystalline α-naphthylurethane; reacetylation of the bisbenzylthiopropanol gave the acetate as a liquid.

As an alternative route to the same compound, the selective benzylation of BAL in aqueous sodium hydroxide, with 2 mol. of benzyl chloride, was investigated. This gave a bisbenzylthiopropanol in excellent yield, but the crystalline α-naphthylurethane was different from that obtained by the other route, and the liquid acetates, also, were not identical. A rearrangement had evidently occurred in one of the preparations, and although it was very improbable that the second method had taken an unusual course it was necessary to provide a rigid proof of the structures of both di-*S*-benzyl compounds. Debenzylation of each with sodium and liquid ammonia, preferably in the presence of some ethanol, took place smoothly and gave the corresponding dimercaptopropanols, which in turn were desulphurised with Raney nickel, and the resulting propanol identified by oxidation and characterisation of the propaldehyde or acetone as the 2 : 4-dinitrophenylhydrazone. In this way the dibenzyl compound obtained by benzylation of BAL gave

* Part XVI, Johary and Owen, preceding paper.

propaldehyde and was therefore the normal product (II); the material from 2 : 3-dibromopropyl acetate, however, gave acetone containing only a trace of aldehyde, and was therefore almost entirely 1 : 3-bisbenzylthiopropan-2-ol (IV). Additional confirmation of this rearrangement was provided by an independent synthesis of (IV).

Fromm, Kapeller, and Taubmann (*Ber.*, 1928, **61**, 1356) described its preparation by reaction of toluene-ω-thiol in alcoholic potassium hydroxide with 1 : 3-dichloropropan-2-ol or epichlorohydrin, but in view of the rearrangement noted above, their method cannot be regarded as structurally definitive. We therefore used the alternative route involving benzylation of 1 : 3-dimercaptopropan-2-ol (V). This dithiol was prepared by Sjöberg (*Ber.*, 1942, **75**, 13) and by Rheinboldt and Tetsch (*Ber.*, 1937, **70**, 677) by a method involving a tedious purification; more convenient was the interaction of 1 : 3-dibromoprop-2-yl acetate with potassium thiolacetate to give crystalline 1 : 3-bisacetylthioprop-2-yl acetate, which on deacetylation with methanolic hydrogen chloride furnished (V). Selective benzylation then gave (IV), the purity of which was established by debenzylation, desulphurisation, and oxidation as before, only acetone being obtained. The α-naphthylurethane was identical with that derived from the abnormal reaction product.

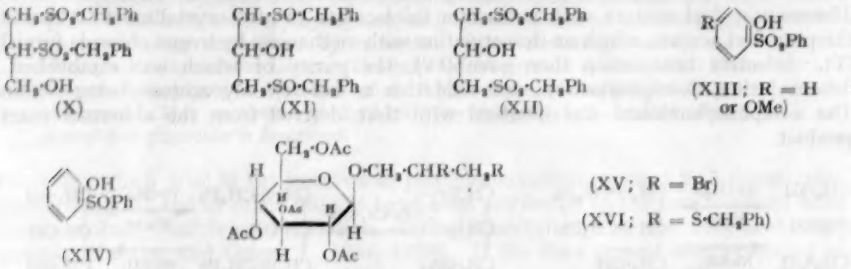


Rearrangement was also shown to occur when 2 : 3-dibromopropanol (VI) was used in place of the acetate in the original reaction; the product was again the 1 : 3-di-*S*-benzyl compound. The mechanism is presumably similar to that which has been shown by Fairbourne to account for the formation of 1 : 3-diethers of glycerol in the reaction of 2 : 3-dibromopropanol with alkoxides (*e.g.*, Fairbourne, Gibson, and Stephens, *J.*, 1932, 1965), and thus involves the intermediate formation of the epoxides (VII) and (VIII) (or the equivalent charged structures). The primary halogen atom may, of course, also undergo direct substitution to some extent. With 2 : 3-dibromopropyl acetate it seems likely that deacetylation occurs first and that subsequent reactions take the above course. Although the formation of a 1 : 3-compound from the acetate could also be explained by acetyl migration from $C_{(1)}$ to $C_{(2)}$, accompanied by substitution at $C_{(1)}$ (cf. Fairbourne *et al.*, *loc. cit.*), such a route is improbable under the conditions used because the intermediate orthoacetate of the type (IX) would interact with the ethanolic solvent and give rise finally to a product with hydroxyl, rather than benzylthio, at $C_{(3)}$ (cf. Winstein, Hess, and Buckles, *J. Amer. Chem. Soc.*, 1942, **64**, 2796).

The usual method for the preparation of BAL is by interaction of 2 : 3-dichloro- or -dibromo-propanol and either sodium or ammonium hydrogen sulphide (Stocken, *loc. cit.*; Ing, *J.*, 1948, 1393), the replacement under these essentially neutral conditions taking a normal course. Occasionally, however, the product has an unusually high toxicity (Stocken, *loc. cit.*) and from our present results it is likely that this is due to the use of too alkaline a reagent, resulting in the formation of an appreciable proportion of the much more toxic 1 : 3-dimercaptopropan-2-ol.

Oxidation of 2 : 3-bisbenzylthiopropanol with hydrogen peroxide in acetic acid afforded the crystalline disulphone (X); the disulphoxide could not be isolated. When, however, 1 : 3-bisbenzylthiopropan-2-ol was treated with the same reagent, interruption of the

reaction after a few minutes gave the disulphoxide (XI), whilst under more vigorous conditions the disulphone (XII) was obtained. Fromm, Kapeller, and Taubmann (*loc. cit.*) claimed to have obtained the latter by permanganate oxidation of 1 : 3-bisbenzylthiopropan-2-ol, but stated that it crystallised from ethanol as an extremely stable monohydrate, which could not be dehydrated by recrystallisation or by drying it at 120°, but only by long boiling with acetic acid. Our product, crystallised either from ethanol or acetic acid, was anhydrous, even when water was present in the solution. Rothstein (*J.*, 1937, 309), who obtained it from a crude 1 : 3-bisbenzylthiopropan-2-ol, also recorded only the anhydrous form. A feature of interest is that the disulphoxide and the disulphone have almost identical melting-points, and a mixture shows no significant depression, so



that identification by mixed melting-point is not conclusive. The two compounds are most readily distinguished by their different solubility properties. Their infrared absorption spectra were determined in Nujol mull by Mr. R. L. Erskine (Organic Spectrographic Laboratory). The disulphone (XII) showed a group of bands with strong maxima at 1309, 1264, 1148, and 1131 cm.$^{-1}$, and weaker peaks at 1406, 1330, 1236, 1210, 1070, 1026, and 1000 cm.$^{-1}$; the hydroxyl band was at 3390 cm.$^{-1}$. The main frequencies are somewhat lower than those characteristic of simple sulphones, for which the maxima are usually in the ranges 1350—1300 and 1155—1140 cm.$^{-1}$ (Barnard, Fabian, and Koch, *J.*, 1949, 2442; Amstutz, Hunsberger, and Chessick, *J. Amer. Chem. Soc.*, **1951**, **73**, 1220). The displacements, and the splitting of the main bands, are probably due to hydrogen bonding with the hydroxyl group; Amstutz *et al.* (*loc. cit.*) found displacement to lower frequencies (1138—1130 cm.$^{-1}$) for two *ortho*-hydroxydiphenyl sulphones (XIII) in which the hydroxyl group has the same relationship to the sulphone group as in (XII). The spectrum of the disulphoxide (XI) was simpler than that of the disulphone, and showed no strong absorption between 1300 and 1100 cm.$^{-1}$; in addition to a hydroxyl peak at 3225 cm.$^{-1}$, the main bands were at 1077 and 1030 cm.$^{-1}$, with weaker peaks at 1005, 995, and 976 cm.$^{-1}$. Barnard *et al.* (*loc. cit.*) found a strong maximum at about 1035 cm.$^{-1}$ with several simple sulphoxides, and observed that in the presence of added methanol a new peak appeared at lower frequency; they concluded that sulphoxides form stronger hydrogen bonds than do sulphones. Amstutz *et al.* (*loc. cit.*) reached a similar conclusion from the behaviour of *o*-hydroxydiphenyl sulphoxide (XIV) which showed no hydroxyl band, only a weak maximum at 1034 cm.$^{-1}$ and a strong band at 994 cm.$^{-1}$.

For a synthesis of the *O*-glucoside of BAL *via* the *S*-benzyl derivative the key compound is 2 : 3-bisbenzylthiopropyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (XVI). Attempts to obtain this by direct condensation of 2 : 3-bisbenzylthiopropanol with acetobromoglucose were unsuccessful owing to incomplete reaction. When 2 : 3-dibromopropyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (XV) was treated with a large excess of the sodium derivative of toluene-ω-thiol in ethanol it was possible to effect complete replacement of the halogen atoms, but deacetylation also occurred. The resulting crude 2 : 3-bisbenzylthiopropyl β-D-glucoside on reacetylation and fractional precipitation gave the required tetra-acetyl compound (XVI). Catalytic deacetylation, followed by debenzylation with sodium and ethanol in liquid ammonia, gave a product with about 85% of the theoretical thiol content, though separation of the free glucoside from the inorganic material was not practicable.

EXPERIMENTAL

2 : 3-*Bisbenzylthiopropanol.*—Benzyl chloride (27·6 g.) was gradually added (25 min.) to a vigorously stirred solution of 2 : 3-dimercaptopropanol (12·4 g.) and sodium hydroxide (9 g.) in water (60 c.c.) under nitrogen; stirring was maintained for a further hour at room temperature and for 1·5 hr. at 100°. The insoluble oil was then extracted from the cold solution with ether, and on distillation gave 2 : 3-*bisbenzylthiopropanol* (23·2 g.), b. p. 215—230° (bath)/0·0001 mm., n_D^{18} 1·6150 (Found: C, 66·8; H, 6·7; S, 21·4. $C_{17}H_{20}OS_2$ requires C, 67·1; H, 6·6; S, 21·05%). The *α-naphthylurethane* (prepared by heating it with α-naphthyl *iso*cyanate for 7 hr. at 90°) after crystallisation from benzene–petroleum (b. p. 60—80°) had m. p. 80—82° (Found: C, 70·7; H, 5·8; N, 3·0; S, 12·9. $C_{28}H_{27}O_2NS_2$ requires C, 71·0; H, 5·75; N, 3·0; S, 13·5%). Acetylation of 2 : 3-bisbenzylthiopropanol with acetic anhydride and sodium acetate at 100° gave the *acetate*, b. p. 220—230° (bath)/0·0006 mm., n_D^{19} 1·5856 (Found: Ac, 12·2. $C_{19}H_{22}O_2S_2$ requires Ac, 12·4%).

Debenzylation. Sodium (6 g.), in small pieces, was added to a stirred solution of 2 : 3-bisbenzylthiopropanol (8·8 g.) and ethanol (10 c.c.) in liquid ammonia (*ca.* 250 c.c.). A vigorous evolution of gas occurred, and the blue colour produced by each addition disappeared rapidly in the early stages, but persisted towards the end. The ammonia was then evaporated off on the water-bath, and the residue was treated with crushed ice (100 g.) and 10% sodium hydroxide solution (20 c.c.). Non-thiol material was removed by ether-extraction, and the alkaline solution was then acidified at 0° with concentrated hydrochloric acid and continuously extracted with ether for several hours; distillation of the oil so obtained gave 2 : 3-dimercaptopropanol (2·2 g., 61%), b. p. 90°/2 mm., n_D^{23} 1·5654 (purity by iodine titration, 95%). A portion (0·5 g.) of this product was heated on the steam-bath for 4 hr. with water (30 c.c.) and Raney nickel (*ca.* 5 g.). The filtered solution was then boiled in a distillation flask during the addition of a 6% solution of sodium dichromate in 25% sulphuric acid (10 c.c.). The distillate was collected in aqueous 2 : 4-dinitrophenylhydrazine sulphate and gave propaldehyde 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 154—156°. Chromatography of the crude derivative failed to indicate the presence of any other compound.

In carrying out the debenzylation in the absence of ethanol, difficulty was experienced owing to the formation of a coating around the sodium; this was overcome by transferring under pressure a solution of sodium (4·5 g.) in liquid ammonia (75 c.c.) into a solution of 2 : 3-bisbenzylthiopropanol (12 g.) in liquid ammonia (325 c.c.). The product on distillation gave 2 : 3-dimercaptopropanol (3·5 g.), b. p. 114—115°/10 mm., n_D^{21} 1·5720 (purity by iodine titration, 99%).

1 : 3-*Dibromoprop-2-yl Acetate.*—1 : 3-Dibromopropan-2-ol (*Org. Synth.*, Coll. Vol. II, 308) (25 g.) was heated with acetic anhydride (25 g.) for an hour at 130—140°. Excess of anhydride and acetic acid was then removed under reduced pressure and the residue was stirred with aqueous sodium hydrogen carbonate. The insoluble oil was isolated by ether extraction, and on distillation gave the acetate (27 g.), b. p. 106—108°/9 mm., 115—117°/20 mm., n_D^{18} 1·5037 (Found: C, 22·8; H, 3·2. Calc. for $C_5H_8O_2Br_2$: C, 23·1; H, 3·1%). Previous workers, using acetyl chloride, recorded b. p. 228° (Aschan, *Ber.*, 1890, **23**, 1827) and b. p. 120°/15 mm., n_D^{18} 1·5141 (Andreeva and Chernov, *Chem. Abs.*, 1940, **34**, 6572). The acetate slowly decomposes, with liberation of acetic acid, when kept.

1 : 3-*Bisacetylthioprop-2-yl Acetate.*—When freshly prepared 1 : 3-dibromoprop-2-yl acetate (20 g.), potassium thiolacetate (23 g.), and ethanol (100 c.c.) were warmed together, a vigorous reaction occurred. After this had subsided the mixture was heated and stirred on the steam-bath for 90 min., and then concentrated under reduced pressure. The residue was diluted with water (100 c.c.) and extracted with ether to give 1 : 3-*bisacetylthioprop-2-yl acetate* (16·8 g.), b. p. 140—145°/0·08 mm., which solidified; recrystallisation from benzene–petroleum (b. p. 60—80°) gave needles, m. p. 46—48° (Found: C, 43·2; H, 5·8; S, 25·9. $C_9H_{14}O_4S_2$ requires C, 43·2; H, 5·6; S, 25·6%).

1 : 3-*Dimercaptopropan-2-ol.*—The above triacetyl compound (10 g.) was boiled under reflux for 2 hr. in methanol (75 c.c.) and concentrated hydrochloric acid (4 c.c.). The solvent was then removed under reduced pressure and the residue, after several evaporations with small amounts of benzene, was distilled to give 1 : 3-dimercaptopropan-2-ol (4·2 g., 85%), b. p. 68—69°/0·8 mm., n_D^{23} 1·5696 (purity by iodine titration, 99%). Rheinboldt and Tetsch (*Ber.*, 1937, **70**, 675) give b. p. 94°/12 mm.; Sjöberg (*Ber.*, 1942, **75**, 13) gives b. p. 82°/1·5 mm., 72°/0·7 mm., n_D^{20} 1·5700.

1 : 3-*Bisbenzylthiopropan-2-ol.*—Treatment of 1 : 3-dimercaptopropan-2-ol (3·5 g.) with

benzyl chloride (7·5 g.), sodium hydroxide (2·5 g.), and water (15 c.c.), as described for the 1 : 2-isomer, gave 1 : 3-bisbenzylthiopropan-2-ol (6·1 g., 75%), b. p. 230—250° (bath)/0·0005 mm., n_D^{22} 1·6100 (Found : C, 66·8; H, 6·8; S, 21·1. $C_{17}H_{20}OS_2$ requires C, 67·1; H, 6·6; S, 21·05%). The *α-naphthylurethane* crystallised from benzene–petroleum (b. p. 60—80°) in fibrous needles, m. p. 85° (Found : C, 71·0; H, 5·9; N, 2·8; S, 12·8. $C_{28}H_{27}O_2NS_2$ requires C, 71·0; H, 5·75; N, 3·0; S, 13·5%); the *acetate* (acetic anhydride–sodium acetate) was an oil, b. p. 205—230° (bath)/0·0001 mm., n_D^{21} 1·5830 (Found : C, 65·9; H, 6·6; S, 18·4. $C_{19}H_{22}O_2S_2$ requires C, 65·9; H, 6·4; S, 18·5%).

Reaction of 2 : 3-*Dibromopropyl Acetate with Toluene-ω-thiol.*—Freshly distilled toluene-ω-thiol (32 g.) was added to ethanolic sodium ethoxide [from sodium (5·85 g.) in ethanol (150 c.c.)] under nitrogen. The solution was stirred at 70° during the rapid addition of 2 : 3-dibromopropyl acetate (33 g.), and was then heated on the steam-bath under reflux; it became neutral in 15 min., and after 2 hr. it was cooled, filtered from sodium bromide, and concentrated under reduced pressure. Ether and water were added to the residue, and the ethereal layer was dried and evaporated to an oil (27 g.) (Found : Ac, 1·6%); almost complete deacetylation had evidently occurred. It was fractionated at 195—215° (bath)/0·0008 mm., n_D^{21} 1·6021—1·6090. The lower-boiling fractions partly crystallised, and on trituration with methanol gave dibenzyl disulphide, m. p. and mixed m. p. 69—70°. A portion (4·9 g.) of the higher-boiling material was dissolved in dry methanol containing a trace of sodium methoxide and set aside overnight to complete the deacetylation; the product on distillation gave a main fraction (3·3 g.) of a bisbenzylthiopropanol, b. p. 220—225° (bath)/0·0008 mm., n_D^{21} 1·6057 (Found : C, 67·0; H, 6·9; S, 21·4. Calc. for $C_{17}H_{20}OS_2$: C, 67·1; H, 6·6; S, 21·05%). Reacetylation with acetic anhydride and sodium acetate gave a bisbenzylthiopropyl acetate, b. p. 220—225° (bath)/0·0001 mm., n_D^{22} 1·5811 (Found : C, 66·0; H, 6·7; S, 18·3. Calc. for $C_{19}H_{22}O_2S_2$: C, 65·9; H, 6·4; S, 18·5%). The bisbenzylthiopropanol gave an α-naphthylurethane which after recrystallisation from benzene–petroleum (b. p. 60—80°) had m. p. 85—86°, not depressed by the authentic derivative of 1 : 3-bisbenzylthiopropan-2-ol, but depressed to 68—76° by the 1 : 2-isomer.

Proof of structure. The above bisbenzylthiopropanol (9 g.) in liquid ammonia (250 c.c.) containing ethanol (10 c.c.) was treated with sodium, added in small pieces, with stirring, until a permanent blue colour was obtained (6·5 g.). The product, isolated as described for the 1 : 2-compound, on distillation gave the dithiol (3·1 g., 82%), b. p. 75—77°/1·8 mm., n_D^{22} 1·5638 (purity by iodine titration, 96%). A portion (1·0 g.) of this was desulphurised with a suspension of Raney nickel (*ca.* 10 g.) in boiling water (20 c.c.) under reflux for 2 hr. The solution was filtered and distilled during the addition of a solution of sodium dichromate (1 g.) in 4N-sulphuric acid (10 c.c.); 20 c.c. of distillate were collected. A portion (1 c.c.) gave a weakly positive test for an aldehyde with Schiff's reagent. The remainder of the distillate was treated with aqueous 2 : 4-dinitrophenylhydrazine sulphate, and gave acetone 2 : 4-dinitrophenylhydrazone (0·24 g.), m. p. and mixed m. p. 124—126°.

Reaction of 2 : 3-*Dibromopropanol with Toluene-ω-thiol.*—Interaction of 2 : 3-dibromopropanol (8·6 g.), toluene-ω-thiol (10 g.), sodium (1·85 g.), and ethanol (40 c.c.) for 2 hr. under reflux, followed by working-up as described above, gave an oil (12·7 g.), b. p. 205—220°/0·0001 mm., n_D^{20} 1·6085—1·6107, consisting essentially of 1 : 3-bisbenzylthiopropan-2-ol; it readily gave the α-naphthylurethane, m. p. and mixed m. p. 84—86°.

2 : 3-*Bisbenzylsulphonylpropanol.*—30% Hydrogen peroxide (2 c.c.) was added to a solution of 2 : 3-bisbenzylthiopropanol (0·65 g.) in acetic acid (2·5 c.c.); the mixture became hot. After 5 min., more peroxide (1 c.c.) was added, and the solution was heated on the steam-bath for 30 min., then cooled and diluted with water. The solid was collected and washed with water; recrystallisation from ethanol gave the *disulphone* (0·6 g.) as small needles, m. p. 171° (Found : C, 55·7; H, 5·8; S, 17·4. $C_{17}H_{20}O_5S_2$ requires C, 55·4; H, 5·5; S, 17·4%). Omission of the heating on the steam-bath (compare the 1 : 3-isomer, below) gave an oily product which could not be purified.

1 : 3-*Bisbenzylsulphinylpropan-2-ol.*—30% Hydrogen peroxide (2 c.c.) was added to a solution of 1 : 3-bisbenzylthiopropan-2-ol (0·55 g.) in acetic acid (2 c.c.). The mixture, which became very hot, was set aside for 5 min. and then poured into water. The precipitate (0·6 g.) was washed and recrystallised from a small volume of ethanol, giving the *disulphoxide* as microcrystals, m. p. 212° (Found : C, 60·3; H, 6·2; S, 19·2. $C_{17}H_{20}O_3S_2$ requires C, 60·7; H, 6·0; S, 19·05%). Infrared absorption : see p. 1304.

1 : 3-*Bisbenzylsulphonylpropan-2-ol.*—The preceding experiment was repeated, but the reaction mixture was treated with a further quantity (1 c.c.) of 30% hydrogen peroxide and

heated on the steam-bath for 35 min. Some solid had then appeared, and more was precipitated on cooling and dilution with water. Part of the crude product (total yield, 0·6 g.) was recrystallised from acetic acid, forming short needles, m. p. 210° (Found: C, 55·5; H, 5·6; S, 17·4. Calc. for $C_{17}H_{30}O_5S_2$: C, 55·4; H, 5·5; S, 17·4%), and the remainder was recrystallised from a large volume of ethanol forming shining plates, m. p. 210° (Found: C, 55·3; H, 5·7%). A mixed m. p. with the disulphoxide was 208—209°. The disulphone, unlike the disulphoxide, is only very sparingly soluble in boiling ethanol. Infrared absorption: see p. 1304.

2 : 3-*Bisbenzylthiopropyl* 2 : 3 : 4 : 6-*Tetra*-O-*acetyl*-β-D-*glucoside*.—A solution of 2 : 3-dibromopropyl 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucoside (15 g.) (Fischer, *Z. physiol. Chem.*, 1920, **108**, 3) and toluene-ω-thiol (15 g.) in ethanolic sodium ethoxide [from sodium (2·75 g.) and ethanol (65 c.c.)] was stirred and boiled under reflux for 6 hr. under nitrogen. The precipitated sodium bromide (4·5 g.) was filtered off, and the filtrate was boiled for a further 2 hr., but no more solid separated. It was neutralised with carbon dioxide, concentrated under reduced pressure, and then diluted with water. The emulsion was extracted successively with (i) petroleum (b. p. 60—80°), which removed unchanged toluene-ω-thiol (6 g.); (ii) 1 : 1 benzene–petroleum, which removed some dibenzyl disulphide; and (iii) benzene, which gave a pale brown glass (6·6 g.). The last substance was partly purified by precipitation, as an oil, from benzene solution by addition of ether; it was dried at 100°/0·0001 mm. (Found: C, 55·6; H, 5·9; S, 12·0; Ac, 0·0%), and reacetylated by treatment of a portion (2·6 g.) with acetic anhydride (15 c.c.) and sodium acetate (2 g.) for 3 hr. at 100°. Concentration under reduced pressure, addition of water, neutralisation with sodium hydrogen carbonate, and extraction with ether gave an oil (3·5 g.) which was dissolved in hot ethanol (7 c.c.). The oil which separated from the cooled solution was subjected to two further reprecipitations from ethanol, and was finally dried at 100°/0·001 mm. to give 2 : 3-*bisbenzylthiopropyl* 2 : 3 : 4 : 6-*tetra*-O-*acetyl*-β-D-*glucoside* (2·95 g.) as a pale yellow oil, n_D^{23} 1·5360 (Found: C, 58·1; H, 6·3; S, 9·4; Ac, 28·1. $C_{31}H_{38}O_{10}S_2$ requires C, 58·7; H, 6·0; S, 10·1; Ac, 27·6%).

Deacetylation and debenzylation. The above product (1·5 g.) in methanolic sodium methoxide (0·2 g. of sodium in 20 c.c. of methanol) was set aside overnight. The solvent was then removed under reduced pressure and the residue was treated with water and benzene. Evaporation of the benzene extract gave the deacetylated glucoside as a pale yellow glass (0·6 g.), which was dissolved in ethanol (1·5 c.c.) and liquid ammonia (*ca.* 30 c.c.). Sodium (1·2 g.) was gradually added, in small pieces, to the stirred solution, until a permanent blue colour was produced. The ammonia was then boiled off, and the residue was dissolved in ethanol and 2N-hydrochloric acid and titrated with iodine (Found: thiol-S, calc. as free dimercaptopropyl glucoside, 11·8. Calc. for $C_{23}H_{30}O_6S_2$: thiol-S, 13·8%).

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Dithiols. Part XVIII. Some Water-soluble Derivatives Containing the Sulphonic Acid Group.*

By N. S. JOHARY and L. N. OWEN.

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The syntheses of water-soluble salts of 2 : 3-dimercaptopropanesulphonic acid and of a 2′ : 3′-dimercaptopropylbenzenesulphonic acid are described. Pure prop-2-ene-1-sulphonic acid has been prepared.

THE syntheses of water-soluble derivatives of 2 : 3-dimercaptopropanol (BAL), described in some of the earlier papers in this series, have been mainly concerned with polyhydroxy-compounds. The present investigation had as its initial object the synthesis of 2 : 3-dimercaptopropanesulphonic acid, which either as free acid or sodium salt (IV) would be

* Part XVII, preceding paper.

expected to possess the antiarsenical properties associated with the presence of the vicinal dithiol grouping, and to be readily soluble in water.

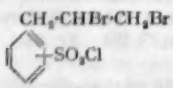
No dimercaptoalkanesulphonates have hitherto been reported. Lipovich (*Zhur. priklad. Khim.*, **1945**, **18**, 718) described the formation, in solution, of three simple sodium monomercaptoalkanesulphonates, but the only compound of this type claimed to have been isolated is sodium 4-mercaptobutane-2-sulphonate (Helberger, Manecke, and Heyden, *Annalen*, 1949, **565**, 22); the purity of the latter, however, was not stated and cannot be assessed in the absence of any recorded thiol value, because the presence of even a considerable proportion of the corresponding disulphide would have little effect on the carbon and hydrogen figures, which were the only analyses given.

Because the free dimercapto-acid would probably lactonise to form the thio-sultone, experiments were directed towards the synthesis of the sodium and the potassium salt. Sodium prop-2-ene-1-sulphonate (I), as prepared by interaction of allyl bromide and sodium sulphite (Belous and Postovskii, *Chem. Abs.*, 1951, **45**, 2391), is obtained as a double salt with sodium bromide, from which the halide can be removed only by tedious recrystallisation. The crude material, however, although insoluble in aprotic solvents is soluble in acetic acid, and it then reacts smoothly with bromine to give sodium 2 : 3-dibromopropanesulphonate (II), which is relatively easily freed from the accompanying

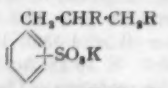
$CH_2{:}CH{\cdot}CH_2{\cdot}SO_3Na$ (I)

$CH_2R{\cdot}CHR{\cdot}CH_2{\cdot}SO_3Na$ (II; R = Br), (III; R = SAc), (IV; R = SH)

$EtO{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}SO_3Et$ (V)



(VI)



(VII; R = Br) (VIII; R = SH)

sodium bromide. When this product was treated with sodium thiolacetate in boiling ethanol, a mixture of sodium salts was obtained, from which the newly-formed sodium bromide was again removed by fractional crystallisation. The bromide-free material so obtained was not the pure bisthiolacetate (III), but was contaminated with the partly deacetylated compound, a circumstance which was not a serious hindrance as the product could be used as such for the final stage of deacetylation. This was rapid in ethanolic sodium ethoxide, but the free dithiol could not be separated from other sodium salts either by crystallisation or by ion-exchange methods. Deacetylation with hot aqueous hydrochloric acid was also unsuccessful, owing to the formation of some sodium chloride which could not be entirely removed, but by hydrolysis of the bisthiolacetate with aqueous acetic acid the pure sodium 2 : 3-dimercaptopropanesulphonate (IV) was obtained.

Only two alkenesulphonic acids have been obtained in the free state, *viz.* ethylenesulphonic acid (*inter al.*, U.S.P. 2,619,452, *Chem. Abs.*, 1953, **47**, 9342; Snyder, Anderson, and Hallada, *J. Amer. Chem. Soc.*, 1951, **73**, 3258) and prop-1-ene-1-sulphonic acid (Lambert and Rose, *J.*, 1949, 46). We have now obtained prop-2-ene-1-sulphonic acid by hydrolysis of its acid chloride, prepared from the crude sodium salt (I); the pure sodium and potassium salts are thus made easily available by subsequent neutralisation of the acid. Addition of bromine to a solution of the potassium salt in acetic acid afforded potassium 2 : 3-dibromopropanesulphonate, which with potassium thiolacetate behaved similarly to the sodium analogue and gave a bisthiolacetate mixed with partly deacetylated material. Complete deacetylation was effected by mild acid hydrolysis, though in this case the free dithiol was not obtained pure.

Other approaches to some of the intermediates were investigated. The attempted conversion of prop-2-ene-1-sulphonyl chloride into the ester, by reaction with ethanol in excess of pyridine, gave only water-soluble products, but when only one mol. of pyridine was used the ethyl ester was obtained in excellent yield; it underwent very rapid hydrolysis when heated with water. Reaction of the sulphonyl chloride in ether with ethanol and potassium hydroxide resulted in addition to the double bond and gave ethyl 3-ethoxypropanesulphonate (V). With bromine in carbon tetrachloride, ethyl prop-2-ene-1-sulphonate gave ethyl 2 : 3-dibromopropane-1-sulphonate; the reaction occurred readily

only in bright sunlight. When the dibromo-ester reacted with potassium thiolacetate, the ester group was destroyed, and the product contained only potassium salts, a result clearly due to the alkylating properties of sulphonic esters.

Attention was next turned to the synthesis of an aromatic analogue. Chlorosulphonation of 2′ : 3′-dibromopropylbenzene gave an analytically pure 2′ : 3′-dibromopropylbenzenesulphonyl chloride (VI) as a liquid, possibly a mixture of isomers. Hydrolysis of the acid chloride with boiling aqueous ethanol did not affect the dibromide group, and neutralisation of the resulting acid afforded a pure potassium 2′ : 3′-dibromopropylbenzenesulphonate (VII). With potassium thiolacetate this gave a potassium 2′ : 3′-bisacetylthiopropylbenzenesulphonate, from which a potassium 2′ : 3′-dimercaptopropylbenzenesulphonate (VIII) was obtained by deacetylation with aqueous acetic acid.

All the sodium and the potassium sulphonates encountered in this investigation were freely soluble in water, and the main experimental difficulty was in effecting their complete separation from accompanying inorganic salts.

Experimental

Sodium 2 : 3-*Dibromopropanesulphonate.*—To a solution of crude sodium prop-2-ene-1-sulphonate (Belous and Postovskii, *Chem. Abs.*, 1951, **45**, 2391) (15 g.) in acetic acid (50 c.c.), bromine (17 g.) in acetic acid (50 c.c.) was added dropwise during 30 min. at 10—15°. The solution, which still contained free bromine, was concentrated under reduced pressure and then stirred with ether (100 c.c.) to precipitate the dibromide (29·5 g.). This contained some sodium bromide, but recrystallisation of a portion from 90% *iso*propanol gave *sodium* 2 : 3-*dibromopropanesulphonate* as hard crystals, decomp. *ca.* 250°, readily soluble in water, methanol, and ethanol (Found : C, 11·8; H, 1·9; Br, 52·4; Na, 7·5. $C_3H_5O_3Br_2SNa$ requires C, 11·85; H, 1·7; Br, 52·6; Na, 7·6%).

Sodium 2 : 3-*Bisacetylthiopropanesulphonate.*—The dibromide (24 g.), sodium thiolacetate (20 g.), and ethanol (120 c.c.) were boiled under reflux for 6 hr. Filtration of the hot solution removed sodium bromide (6 g.); the cooled solution deposited the crude bisthiolacetate (17 g.) containing a little sodium bromide, most of which was removed by solution of the solid in boiling dry methanol (125 c.c.), concentration to about half bulk, and addition of dry ethanol (70 c.c.). One further crystallisation of the precipitated solid from methanol gave material which was free from halogen, but the bisthiolacetate contained a small amount of free thiol (Found : C, 26·3; H, 3·8; thiol-S, 1·9. Calc. for $C_7H_{11}O_5S_3Na$: C, 28·6; H, 3·8%). Repeated recrystallisation resulted only in further deacetylation.

Sodium 2 : 3-*Dimercaptopropanesulphonate.*—A solution of the bisthiolacetate (1 g.) in 15% acetic acid (30 c.c.) was heated on the steam-bath for 40 hr. in nitrogen, the thiol value then having risen to 84% of the theoretical. The solution was freeze-dried at 0·05 mm., and the residue was triturated with ethanol (10 c.c.); the solid (0·6 g.) was collected and dried in vacuum (P_2O_5) (Found : C, 18·1; H, 3·8; Na, 10·9; thiol-S, 23·6%). A portion (175 mg.) was dissolved in water (0·5 c.c.) containing a trace of acetic acid, and the solution filtered, diluted with ethanol (3 c.c.), and cooled to 0°; a solid (60 mg.), which crystallised, had a low thiol content and was rejected. The residual solution was concentrated in a vacuum desiccator (NaOH), and was then stirred with ethanol (3 c.c.) and a trace of acetic acid, giving leaflets of the *dithiol* (55 mg.), which were collected by centrifugation, washed with ethanol, and dried (P_2O_5) (Found : C, 17·6; H, 3·7; Na, 11·0; thiol-S, 31·0. $C_3H_7O_3S_3Na$ requires C, 17·1; H, 3·35; Na, 10·9; thiol-S, 30·5%).

Prop-2-ene-1-sulphonyl Chloride.—A mixture of crude sodium prop-2-ene-1-sulphonate (100 g.) and phosphorus oxychloride (170 g.) was boiled under reflux with occasional shaking for 3 hr. Most of the remaining oxychloride was then removed on the steam-bath at 120 mm., and the residue, suspended in pure chloroform (250 c.c.), was gradually treated with crushed ice (200 g.). The washed and dried chloroform layer on evaporation gave the sulphonyl chloride, which distilled as a colourless oil (58·5 g., 61%), b. p. 74—76°/15 mm., n_D^{20} 1·4767. Belous and Postovskii (*loc. cit.*), who obtained a 33% yield, reported b. p. 73—75°/12·5 mm., n_D^{14} 1·4730.

Prop-2-ene-1-sulphonic Acid.—When the acid chloride (15 g.) was heated and stirred with water (50 c.c.) on the steam-bath, the mixture became homogeneous in 30 min. It was cooled, extracted once with ether (the extract being rejected), and then evaporated under reduced pressure to give the *sulphonic acid* as a viscous, hygroscopic liquid (12 g.), which could be

distilled in gram portions at *ca.* 180° (bath)/0·0001 mm.; it then had n_D^{20} 1·4620 (Found: C, 29·45; H, 5·2. $C_3H_6O_3S$ requires C, 29·5; H, 4·95%). Neutralisation in aqueous solution with pure potassium hydroxide, and evaporation to dryness, gave the *potassium salt*, which crystallised from methanol in shining leaflets, decomp. *ca.* 240° (Found: C, 22·5; H, 3·2; K, 25·0. $C_3H_5O_3SK$ requires C, 22·5; H, 3·1; K, 24·4%).

Potassium 2 : 3-*Dibromopropanesulphonate*.—The above potassium salt (20 g.) was treated in acetic acid (100 c.c.) with bromine (24 g.) in acetic acid (50 c.c.), and the product was isolated as for the sodium compound. It was crystallised first from methanol–ethanol (1 : 1), and then from methanol, to give the *dibromide*, decomp. *ca.* 260° (Found: C, 11·9; H, 1·9; Br, 49·6. $C_3H_5O_3Br_2SK$ requires C, 11·3; H, 1·6; Br, 49·95%). Unlike the sodium compound it was only sparingly soluble in ethanol.

Potassium 2 : 3-*Bisacetylthiopropanesulphonate*.—Reaction of the dibromide (10 g.) with potassium thiolacetate (8·5 g.) in boiling ethanol (60 c.c.), as for the sodium salt, gave a solid (8·4 g.) containing some potassium bromide; the latter was removed by recrystallisation from ethanol, but the resulting bisthiolacetate was partly deacetylated (Found: C, 25·7; H, 3·7; K, 15·4; thiol-S, 3·9. Calc. for $C_7H_{11}O_5S_3K$: C, 27·1; H, 3·6; K, 12·6%).

Deacetylation. The crude bisthiolacetate (2 g.) was heated with acetic acid (3 c.c.) and water (17 c.c.) for 48 hr. at 100° in nitrogen. The thiol content reached only 61% of the theoretical (cf. the corresponding sodium salt) and fractional crystallisation of the isolated salt gave material (Found: C, 17·7; H, 3·4; S, 37·9; thiol-S, 22·5; K, 18·2. Calc. for $C_3H_7O_3S_2K$: C, 15·9; H, 3·1; S, 42·5; thiol-S, 28·3; K, 17·3%) which could not be completely purified.

Ethyl Prop-2-ene-1-sulphonate.—Dry pyridine (7·9 g.) in pure chloroform (10 c.c.) was slowly added (15 min.) to a stirred solution of prop-2-ene-1-sulphonyl chloride (13·9 g.) in dry ethanol (5 g.) and pure chloroform (15 c.c.) at −5°. The mixture was kept at −5° for a further 15 min., then warmed to 20° and kept for 20 min. After the addition of crushed ice (20 g.) the chloroform layer was separated, washed once with water, dried ($CaCl_2$), and evaporated to an oil, which on distillation furnished the *ethyl ester* (12·6 g.), b. p. 53—55°/0·1 mm., 80—82°/0·5 mm., n_D^{25} 1·4410 (Found: C, 40·0; H, 6·9; S, 21·15. $C_5H_{10}O_3S$ requires C, 40·0; H, 6·7; S, 21·3%). This was insoluble in cold water, but was rapidly decomposed by boiling water.

Ethyl 3-*Ethoxypropanesulphonate*.—Finely powdered potassium hydroxide (1·5 g.) was added in small portions to a stirred mixture of prop-2-ene-1-sulphonyl chloride (1·4 g.), dry ethanol (0·48 g.), and dry ether (15 c.c.) at 0° to −5°. Stirring was maintained for a further 2 hr. at 0°, and the mixture was then set aside at room temperature overnight. Ice (5 g.) was added, and the ether layer was separated, dried (Na_2SO_4), and evaporated to an oil (0·35 g.), consisting essentially of *ethyl* 3-*ethoxypropanesulphonate*, b. p. 126—132°/18 mm., n_D^{22} 1·4352 (Found: C, 42·6; H, 7·9; S, 17·1; EtO, 42·6. $C_7H_{16}O_4S$ requires C, 42·85; H, 8·2; S, 16·3; OEt, 45·9%). The material was slightly unsaturated and the analytical figures are compatible with the presence of 5—10% of the unsaturated ethyl ester.

Ethyl 2 : 3-*Dibromopropanesulphonate*.—Bromine (11 g.) in carbon tetrachloride (25 c.c.) was added to ethyl prop-2-ene-1-sulphonate (10 g.) in carbon tetrachloride (25 c.c.) in strong sunlight. The reaction (which in the absence of sunlight was very slow) was complete in 3 hr., and evaporation of the solvent and distillation of the residue gave the *dibromo-ester* (18·9 g.), b. p. 114—118°/0·001 mm., n_D^{21} 1·5182, n_D^{22} 1·5142 (Found: C, 19·7; H, 3·35; Br, 51·4. $C_5H_{10}O_3Br_2S$ requires C, 19·4; H, 3·25; Br, 51·6%).

Reaction with potassium thiolacetate. The dibromo-ester (6·2 g.), potassium thiolacetate (5·5 g.), and ethanol (25 c.c.) were boiled under reflux for 4 hr. Most of the ethanol was then removed under reduced pressure and the residue was shaken with water (15 c.c.) and chloroform (40 c.c.). The chloroform layer was removed and the aqueous portion was extracted once more with chloroform. Evaporation of the combined extracts gave a sticky solid (0·9 g.) which was extracted with boiling ethanol (40 c.c.). An insoluble residue (0·2 g.) was rejected, and the filtrate was cooled; a pale yellow hygroscopic solid (0·7 g.) was deposited. This had unusual solubility properties, being soluble in water and in chloroform, but insoluble in cold ethanol. It was probably a mixture of the potassium salts of 2 : 3-bisacetylthio- and 3-acetylthio-2-bromopropanesulphonic acids (Found: C, 22·0; H, 3·0; S, 23·6; Br, 13·6; K, 15·1. Calc. for $C_7H_{11}O_5S_3K$: C, 27·1; H, 3·6; S, 31·0; K, 12·6. Calc. for $C_5H_8O_4BrS_2K$: C, 19·05; H, 2·6; Br, 25·35; S, 20·3; K, 12·4%).

Chlorosulphonation of 2′ : 3′-*Dibromopropylbenzene*.—The dibromo-hydrocarbon (Huston and Sagar, *J. Amer. Chem. Soc.*, 1926, **48**, 1955) (5 g.) in pure chloroform (20 c.c.) was added slowly (10 min.) to a stirred mixture of chlorosulphonic acid (10 c.c.) and pure chloroform (15 c.c.) at 0°. After being kept for an hour at room temperature, the solution was treated with ice (100 g.);

the chloroform layer was washed with water, dried (Na_2SO_4), and evaporated to a viscous oil, which on distillation furnished 2′ : 3′-dibromopropylbenzenesulphonyl chloride (possibly a mixture of isomers) (5 g.), b. p. 210—220° (bath)/0·0002 mm., n_D^{21} 1·6052 (Found : C, 28·6; H, 2·6; S, 8·55. Calc. for $C_9H_9O_2ClBr_2S$: C, 28·7; H, 2·4; S, 8·5%).

Potassium 2′ : 3′-Dibromopropylbenzenesulphonate.—A solution of the acid chloride (17 g.) in ethanol (100 c.c.) was boiled for 12 hr. under reflux. Water (20 c.c.) was then added, and the heating was maintained for a further 4 hr., after which the solution was evaporated under reduced pressure, the last traces of hydrochloric acid being removed by several evaporations from ethanol. The residual oil was dissolved in water (600 c.c.) and freed from a small amount of insoluble material by one extraction with ether (50 c.c.), the extract being discarded. The aqueous solution was then neutralised (phenolphthalein) with potassium hydroxide and evaporated to dryness at 15 mm.; the solid residue was triturated with ethanol (50 c.c.) and collected by filtration (yield, 10·6 g.). Recrystallisation from 90% ethanol gave pearly leaflets of the *potassium salt* (Found : Br, 40·0%. $C_9H_9O_3Br_2SK$ requires Br, 40·4%).

Potassium 2′ : 3′-Bisacetylthiopropylbenzenesulphonate.—The above dibromo-salt (7·8 g.) and potassium thiolacetate (5·8 g.) were boiled in ethanol (50 c.c.) for 6 hr. under nitrogen. The mixture was then diluted with ethanol (20 c.c.), heated to boiling, and filtered hot, and the solid was washed with hot ethanol (30 c.c.). Cooling the combined filtrates precipitated the crude product (3·3 g.), which contained a little potassium bromide; the latter was removed by crystallisation of the material from dry methanol, from which the bisthiolacetate separated as microcrystals (Found : C, 38·9; H, 3·8; K, 11·1. Calc. for $C_{13}H_{15}O_4S_3K$: C, 40·4; H, 3·9; K, 10·1%). The analytical figures indicate slight deacetylation.

Potassium 2′ : 3′-Dimercaptopropylbenzenesulphonate.—The bisacetylthio-compound (0·75 g.), acetic acid (2 c.c.), and water (18 c.c.) were heated under reflux on the steam-bath for 2 days under nitrogen, the thiol value of the solution then having attained 85% of the theoretical for complete deacetylation. The solution was then freeze-dried at 0·05 mm., and the residue was triturated with dry ethanol (3 c.c.). Filtration gave the *dithiol* (0·32 g.), a portion of which was recrystallised from ethanol–water–acetic acid (16 : 3 : 1) (Found : C, 35·8; H, 3·9; S, 32·0; K, 13·05; thiol-S, 18·8. $C_9H_{11}O_2S_3K$ requires C, 35·7; H, 3·7; S, 31·8; K, 12·9; thiol-S, 21·2%). The thiol value indicates slight oxidation to disulphide.

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The Characteristic Infrared Absorption Frequencies of Aromatic Trifluoromethyl Compounds.

By R. R. RANDLE and D. H. WHIFFEN.

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The characteristic frequencies of the C–F stretching vibrations of aromatic trifluoromethyl compounds are considered, and the symmetrical vibration shown to absorb strongly near 1321 cm.$^{-1}$ and the antisymmetrical vibrations near 1179 cm.$^{-1}$ and probably near 1140 cm.$^{-1}$.

THE recent review of characteristic absorption frequencies by Bellamy (" The Infrared Spectra of Complex Molecules," Methuen, 1954) has shown that knowledge of the frequencies of the CF_3 group is fragmentary. Since the spectra of 21 compounds containing an aromatic CF_3 group prepared by Pettit and Tatlow (*J.*, 1951, 3459; 1954, 1071) had been measured in another connection, they were examined for evidence relating to the CF_3 group frequencies.

The most useful guide to the spectral region where the frequencies are most likely to be found is the assignment of 1 : 4-bistrifluoromethylbenzene by Ferguson, Mikkelson, Nielsen, and Smith (*J. Chem. Phys.*, 1953, **21**, 1731), who placed the symmetrical frequency at 1320 cm.$^{-1}$ and the antisymmetrical modes at 1180 and 1137 cm.$^{-1}$ in the infrared spectrum. These frequencies are in agreement with the comments of Thompson and Temple (*J.*, 1948, 1432) who found strong bands near 1330 and 1150 cm.$^{-1}$ in such compounds.

The second column of the Table shows the frequencies of the very strong infrared

absorptions near 1321 cm.$^{-1}$ of the compounds listed; in the compounds containing also a nitro-group the band was distinct from that near 1349 cm.$^{-1}$ of this group (Randle and Whiffen, *J.*, 1952, 4153). There can be little doubt about the assignment of these bands to the symmetrical C–F stretching vibrations.

Compound	Frequencies (cm.$^{-1}$) Symm.	Antisymmetrical	
Trifluoromethylbenzene (*a*)	1326	1176	1127
m-Fluorotrifluoromethylbenzene (*a*)	1333	1174	1135
p- ,, ,, (*b*)	1335	1175	1150
p-Bistrifluoromethylbenzene (*a*)	1320	1180	1137
2 : 5-Difluorotrifluoromethylbenzene (*a*)	1325	1190	1149
o-Nitrotrifluoromethylbenzene	1305	1181	1136
m- ,, ,,	1312	1172	1143
p- ,, ,,	1319	1181	1150
o-Trifluoromethylacetanilide	1316	1167	1158
m- ,, ,,	1318	1173	1129
p- ,, ,,	1332	1180	1152
2-Nitro-3-trifluoromethylaniline	1308	1185	1136
4-Nitro-3- ,, ,,	1326	1190	1145
4-Nitro-2- ,, ,,	1319	1181	1145
2-Nitro-3-trifluoromethylacetanilide	1326	1181	1136
4-Nitro-3- ,, ,,	1314	1172	1142
4-Nitro-2- ,, ,,	1315	1181	1135
4-Nitro-3-trifluoromethyldiphenyl	1314	1181	1141
4′- ,, ,,	1328	1172	1136
2′- ,, ,,	1337	1170	1130
4-Amino-3- ,, ,,	1319	1179	1152
4-Acetamido-3- ,,	1324	1190	1141
4 : 4′-Dinitro-3-trifluoromethyldiphenyl	1312	1185	1149
4 : 4′-Dinitro-3 : 3′-bistrifluoromethyldiphenyl	1330	1190	1154
4 : 4′-Diacetamido-3-trifluoromethyldiphenyl	1313	1181	1132
2 : 4′-Diamino-4 : 2′-bistrifluoromethyldiphenyl	1335	1172	1128
Mean and standard deviation	1321 ± 9	1179 ± 7	1140 ± 9

(*a*) A.P.I. project 44. Catalogue of Infrared Spectra. (*b*) Thompson and Temple, *loc. cit.*

Although for an isolated CF_3 group the antisymmetric stretching vibrational mode is degenerate, the aromatic ring will lift this degeneracy and lead to two orthogonal vibrations with changes of dipole moment vector parallel and perpendicular to the ring. The two vibrations will differ only slightly in frequency and, in view of the strongly polar nature of the C–F link, should both be strong in infrared absorption. In agreement with the work of the authors cited above, strong bands were found in the range 1100—1200 cm.$^{-1}$ whose intensities were greater than is common for the in-plane aromatic C–H deformation absorptions usually found in this range. The highest frequency of the observed intense absorptions lies near 1179 cm.$^{-1}$ in each case, whereas the nearest in-plane C–H deformation frequency given by Randle and Whiffen (" Molecular Spectroscopy," Report on the conference held in London in October, 1954, by the Institute of Petroleum) is slightly lower for some substitution types such as *ortho* (band at 1159 ± 7 cm.$^{-1}$), 1 : 2 : 3 (1160 ± 5 cm.$^{-1}$), 1 : 2 : 4 (1151 ± 8 cm.$^{-1}$), although for others, including mono- (1177 ± 8 cm.$^{-1}$), *meta* (1165 ± 6 cm.$^{-1}$), and *para* (1179 ± 7 cm.$^{-1}$), these C–H deformation frequencies overlap the proposed CF_3 range. Of the 26 compounds in the Table, for 11, which include all the 1 : 2 : 3, 1 : 2 : 4, and all but one of the *ortho* cases, the strong band is outside the normal range (taken as twice the standard deviation) of the C–H deformation frequencies of the substitution types involved, and in the remaining 15 cases the frequency is higher than the average value. Together with the strength of the bands and the fact that there are usually other bands which could be the C–H deformation frequencies, this evidence suggests that one of the antisymmetrical vibration frequencies has been correctly located near 1179 cm.$^{-1}$. The second antisymmetrical frequency must lie close to this, and all the compounds show strong absorption between 1170 and 1100 cm.$^{-1}$, but the existence of C–H deformation frequencies in this range makes choice of the CF_3 frequencies difficult. Indeed, it is not certain that only one of the bands involves appreciable C–F stretching, since the vibrational mode which is symmetrical to the plane of the benzene ring may interact with the C–H deformations so that the vibrations are mixed in type and, in particular, the weaker C–H

deformations may borrow intensity from the stronger C–F stretchings. Another explanation of the number of strong bands assumes that some of them are sum-and-difference tones involving the very low CF_3 internal rotation frequency. The most satisfactory average frequency seemed to be 1140 cm.$^{-1}$ as given in the table, but a value nearer 1112 cm.$^{-1}$ is also possible.

Experimental.—The spectra are those of solid films obtained by using the Nujol technique with a Grubb–Parsons single-beam spectrometer with a rock-salt prism.

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*Derivatives of Benzo-1 : 4-dioxan. Part III.**

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[Reprint Order No. 5972.]

Preparation and orientation are given of 3 : 6-dinitropyrocatechol, 5 : 6-dinitro-7-amino-, 5 : 6-dinitro-, and 5 : 8-dinitro-benzo-1 : 4-dioxan, and some nitro-, amino-, and chloro-derivatives thereof.

IN the annexed chart the reactions described in this paper are shown. Most of the conversions were carried out by standard methods.

The following points merit mention. The dinitrobenzo-1 : 4-dioxan obtained by dinitration, either directly or *via* the mononitro-derivative (II), of 6-acetamidobenzo-1 : 4-dioxan (I), followed by deacetylation and deamination, was the 5 : 6-dinitro-derivative (XI), since (i) it is known that in mononitration the first nitro-group enters the 7-position (Heertjes and Revallier, *Rec. Trav. chim.*, 1950, **69**, 262), (ii) the obtained product is not identical with 5 : 7-dinitrobenzo-1 : 4-dioxan described in Part II, and (iii) the diamino-compound (XV) obtained by reduction gave a condensation product with phenanthraquinone, which proves the *ortho*-position of the amino-groups.

Deamination of 7-amino-5 : 6-dinitrobenzo-1 : 4-dioxan (V) was effected in the normal way by diazotisation in sulphuric–acetic acid and boiling with alcohol and copper. Heating the amine with sodium nitrite, alcohol, and hydrochloric acid gave a monochloronitrobenzo-1 : 4-dioxan. This compound was not identical with 6-chloro-7-nitrobenzo-1 : 4-dioxan and proved to be the 6-chloro-5-nitro-derivative (VI), since it was converted *via* the chloro-amine (VII) into 6-chlorobenzo-1 : 4-dioxan (IX) described in Part I, and since the acetyl derivative (VIII) of the chloro-amine was not identical with 5-acetamido-7-chlorobenzo-1 : 4-dioxan prepared from 5-acetamido-7-aminobenzo-1 : 4-dioxan described in Part II.

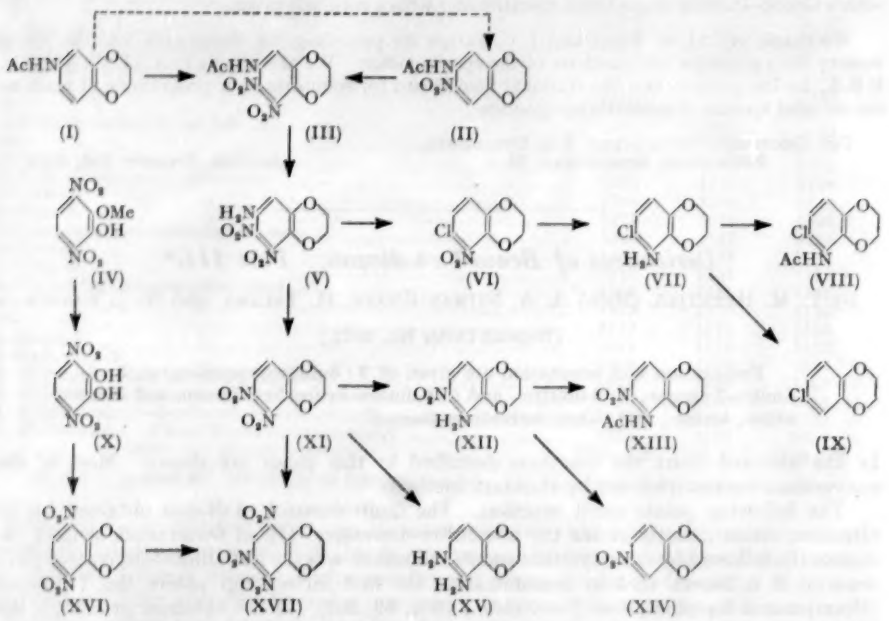
Conversion of 5 : 6-dinitrobenzo-1 : 4-dioxan (XI) into a monoamino-mononitro-derivative could not be realised by partial reduction by the conventional methods (sodium polysulphide, stannous chloride, sodium dithionite, catalytic reduction) : in all cases a mixture of the dinitro- and diamino-derivative was obtained. However, by heating the dinitro-compound with ethanol and concentrated aqueous ammonia at 130—150°, the dinitro-derivative was converted exclusively into 5-amino-6-nitrobenzo-1 : 4-dioxan (XII). The orientation of this compound followed from its conversion into 6-nitrobenzo-1 : 4-dioxan (XIV).

3 : 6-Dinitropyrocatechol (X), not described in the literature, was prepared by boiling 3 : 6-dinitroguaiacol (IV) (Oxford, *J.*, 1926, 2009) with 48% aqueous hydrogen bromide.

* Parts I and II, *J.*, 1954, 18, 1868.

It is worth mention that this method is unsatisfactory for demethylation of the other known dinitro-guaiacols (3 : 4-, 4 : 5-, 5 : 6-).

3 : 6-Dinitropyrocatechol was converted into 5 : 8-dinitrobenzo-1 : 4-dioxan (XVI) by reaction with 1 : 2-dibromoethane in an alkaline solution of glycol. The product was obtained impure, in a poor yield, and was difficult to purify by crystallisation; during the reaction the evolution of nitrogen oxides had been observed; moreover the nitrogen



content of the crystallised compound was far too low; the presence of a monohydroxy-mononitro-compound therefore seemed probable. The crystallised impure 5 : 8-dinitrobenzo-1 : 4-dioxan was therefore dissolved in benzene and washed with a cold 2N-potassium hydroxide solution. This manipulation raised the nitrogen content to nearly the theoretical amount. Owing to the small amounts available the impurity could not be isolated.

5 : 6-Dinitro- and the crude 5 : 8-dinitro-benzo-1 : 4-dioxan on nitration gave the same trinitro-derivative (XVII), which was not identical with 5 : 6 : 7-trinitrobenzo-1 : 4-dioxan (Heertjes, Dahmen, and Wierda, *Rec. Trav. chim.*, 1941, **60**, 569) and must therefore be 5 : 6 : 8-substituted.

Experimental

M. p.s are corrected.

7-Amino-5 : 6-dinitrobenzo-1 : 4-dioxan (V).—Finely powdered 6-acetamidobenzo-1 : 4-dioxan (46 g.; cf. Heertjes and Revallier, *ibid.*, 1950, **69**, 262) was added in portions to a stirred mixture of nitric acid (*d* 1·4; 400 ml.) and nitric acid (*d* 1·52; 100 ml.), kept at 10°. The mixture was diluted with water (500 ml.), and the precipitated *7-acetamido-5 : 6-dinitrobenzo-1 : 4-dioxan* (51 g., 76%) crystallised several times from acetone, or acetone–methanol (1 : 1) or acetone–acetic acid (1 : 1), then having m. p. 230·8—231·0° (Found: N, 14·7, 14·8. $C_{10}H_9O_7N_3$ requires N, 14·8%).

The acetamidonitro-derivative was also prepared from 7-acetamido-6-nitrobenzo-1 : 4-dioxan by nitration with the same nitric acid.

The free *amine* was obtained by boiling 7-acetamido-5 : 6-dinitrobenzo-1 : 4-dioxan (200 g.) with ethanol (750 ml.) and concentrated hydrochloric acid (75 ml.) for 4 hr. The product

separated from the solution on cooling and, when crystallised from ethanol, had m. p. 215·7—216·3° (Found : N, 17·5, 17·5. $C_8H_7O_6N_3$ requires N, 17·4%).

5 : 6-*Dinitrobenzo*-1 : 4-*dioxan* (XI).—A suspension of 7-amino-5 : 6-dinitrobenzo-1 : 4-dioxan (20 g.) in acetic acid (500 ml.) was diazotised with sodium nitrite (17 g.) in concentrated sulphuric acid (200 ml.) at 15°, until the mixture no longer gave a precipitate of the amine on dilution with water (2 hr.). The mixture was poured into absolute ethanol (400 ml.), and copper powder (1 g.) was added. After 24 hr. at room temperature the diazonium compound was completely decomposed. The mixture was diluted with water, and the precipitated crude product (10 g.) collected. A second portion (5·5 g.) of the substance was obtained from the upper layer formed, containing ethyl acetate, by concentrating this to a small volume. The total yield was 82%. **5 : 6-*Dinitrobenzo*-1 : 4-*dioxan*** crystallised in yellow needles, m. p. 185·6—186·1° (from ethanol) (Found : C, 42·3, 42·4; H, 2·8, 2·5; N, 12·4, 12·3. $C_8H_6O_6N_2$ requires C, 42·5; H, 2·7; N, 12·4%).

5 : 6 : 8-*Trinitrobenzo*-1 : 4-*dioxan* (XVII).—5 : 6-Dinitrobenzo-1 : 4-dioxan (2 g.), dissolved in nitric acid (*d* 1·52; 25 ml.), was kept at 10° for ½ hr., then poured into water. The precipitated *trinitro*-derivative was crystallised several times from ethanol and from *iso*butanol, forming yellow needles, m. p. 180·4—181·0° (Found : N, 15·5, 15·3. $C_8H_5O_8N_3$ requires N, 15·5%). The m. p. was depressed on admixture with 5 : 6 : 7-trinitrobenzo-1 : 4-dioxan.

5-*Amino*-6-*nitrobenzo*-1 : 4-*dioxan* (XII).—5 : 6-Dinitrobenzo-1 : 4-dioxan (5 g.) was heated with concentrated aqueous ammonia (5·5 ml.) and ethanol (20 ml.) for 3 hr. in a sealed tube at 130—150°. Cooling the mixture and filtering the crude product from the mother-liquor yielded the quantitative amount of **5-*amino*-6-*nitrobenzo*-1 : 4-*dioxan***, orange needles, m. p. 142·8—143·3° (from ethanol or dilute acetic acid) (Found : N, 14·2, 14·1. $C_8H_8O_4N_2$ requires N, 14·3%).

The nitro-amine was diazotised and boiled with ethanol to decompose the diazonium compound. On dilution with water 6-nitrobenzo-1 : 4-dioxan was precipitated (cf. Heertjes, Dahmen, and Wierda, *ibid.*, 1941, **60**, 569).

On treatment of a solution of 5-amino-6-nitrobenzo-1 : 4-dioxan (0·5 g.) in acetic acid (20 ml.) with acetic anhydride for ½ hr. at 75° and pouring the mixture into water the *acetyl derivative* was precipitated, which crystallised from water as pale yellow needles, m. p. 185·9—186·7° (Found : N, 11·75, 11·7. $C_{10}H_{10}O_5N_2$ requires N, 11·8%).

5 : 6-*Diaminobenzo*-1 : 4-*dioxan* (XV).—5 : 6-Dinitrobenzo-1 : 4-dioxan (5 g.) was heated with concentrated hydrochloric acid (40 ml.), water (20 ml.), and granulated tin (10 g.) at 90° (2 hr.). The mixture was cooled, diluted with water to 150 ml., and treated with enough aqueous potassium hydroxide solution (20%) to redissolve the tin compounds, then extracted with benzene. On evaporation of the benzene from the extract the *diamine* remained as a white crystalline powder (m. p. 101·9—102·9°) which was readily oxidised on contact with air (Found : N, 16·9, 17·1. $C_8H_{10}O_2N_2$ requires N, 16·9%).

Condensation of the base with phenanthraquinone gave a yellow solid, m. p. 292—294°.

6-*Chloro*-5-*nitrobenzo*-1 : 4-*dioxan* (VI).—To a mixture of 7-amino-5 : 6-dinitrobenzo-1 : 4-dioxan (20 g.), ethanol (200 ml.), and concentrated hydrochloric acid (20 ml.), heated to 40°, sodium nitrite (6 g.) was added in portions in 15 min. After ½ hour's boiling the clear solution obtained was cooled and poured into water. The precipitated **6-*chloro*-5-*nitrobenzo*-1 : 4-*dioxan*** (14 g., 78%), after repeated crystallisation from aqueous methanol (1 : 1), had m. p. 75·6—76·3° (Found : C, 44·6; H, 2·9; N, 6·5, 6·6; Cl, 16·25, 16·3. $C_8H_6O_4NCl$ requires C, 44·6; H, 2·8; N, 6·5; Cl, 16·45%).

5-*Amino*-6-*chlorobenzo*-1 : 4-*dioxan* (VII).—(*a*) A solution of 6-chloro-5-nitrobenzo-1 : 4-dioxan (14 g.) in benzene (200 ml.) was hydrogenated in presence of Raney nickel at room temperature. After filtration of the catalyst 5-amino-6-chlorobenzo-1 : 4-dioxan hydrochloride (14 g., 97%) was precipitated by passage of hydrogen chloride through the filtrate.

(*b*) A mixture of 6-chloro-5-nitrobenzo-1 : 4-dioxan (10 g.), concentrated hydrochloric acid (50 ml.), ethanol (50 ml.), and granulated tin (15 g.) was boiled till all the tin had dissolved and the solution gave no precipitate on dilution with water. The mixture was cooled, diluted with water (300 ml.), and basified with sodium hydroxide solution, then extracted with benzene, from which the amine was obtained on evaporation as a yellow oil. The amine slowly oxidises on contact with air.

Treatment of the amine with an excess of acetic anhydride at room temperature and dilution with water gave a precipitate of the *acetyl derivative* (VIII), white needles (from benzene), m. p. 155·9—156·7° (Found : N, 6·0, 6·1. $C_{10}H_{10}O_3NCl$ requires N, 6·15%).

Diazotising the amine and boiling it with ethanol yielded 6-chlorobenzo-1 : 4-dioxan, a

yellow liquid, b. p. 98—102°/4 mm., which on nitration gave 6-chloro-7-nitrobenzo-1 : 4-dioxan, m. p. 161·7—162·2° (see Part I).

The acetyl derivative (VIII) described showed a very strong depression on admixture with 5-acetamido-7-chlorobenzo-1 : 4-dioxan (see below). Because the 6-position of chlorine has been proved above, and moreover the compounds under discussion are not substituted in the 7-position [see the m. p. of the nitro-compound (VI)], the structure as given is proved.

5-Amino-7-chlorobenzo-1 : 4-dioxan.—5-Acetamido-7-aminobenzo-1 : 4-dioxan (0·9 g.) in concentrated hydrochloric acid (3 ml.) and water (5 ml.) was diazotised with a solution of sodium nitrite (0·35 g.) in water (3 ml.) at 10°. The mixture was poured into a solution of cuprous chloride (0·6 g.) in concentrated hydrochloric acid (3 ml.). After 24 hr. at room temperature the diazonium compound was completely decomposed. The precipitated *5-acetamido-7-chlorobenzo-1 : 4-dioxan* was filtered off and crystallised several times from water; it had m. p. 135·6—136·2° (Found: N, 6·1, 6·1. $C_{10}H_{10}O_3NCl$ requires N, 6·15%).

3 : 6-Dinitropyrocatechol (X).—3 : 6-Dinitroguaiacol (5·2 g.; cf. Oxford, *J.*, 1926, 2009) was refluxed with aqueous hydrogen bromide (48%, 52 ml.) for ½ hr. *3 : 6-Dinitropyrocatechol* separated from the liquid in yellow needles. After cooling and dilution with water the product was collected and washed with water (4·6 g., 95%; m. p. 164·5—165·5°). Repeated crystallisations from aqueous ethanol raised the m. p. to 169·4—169·7° (Found: N, 14·0, 14·05. $C_6H_4O_6N_2$ requires N, 14·0%).

5 : 8-Dinitrobenzo-1 : 4-dioxan (XVI).—Condensation of 3 : 6-dinitropyrocatechol with ethylene dibromide was effected as described for the preparation of 5 : 7-dinitrobenzo-1 : 4-dioxan (see Part II). Contrary to analogous condensations, during this reaction the formation of nitrogen oxides was observed. Pouring the reaction mixture in water gave a dark brown precipitate, which was collected and extracted with benzene. The yellow benzene solution was washed with aqueous potassium hydroxide (2N), then with water. After removal of the benzene the remaining *5 : 8-dinitrobenzo-1 : 4-dioxan*, crystallised from ligroin (b. p. 60—80°) or aqueous ethanol (1 : 1), had m. p. 99·6—102·5° (yield 15%) (Found: C, 42·6; H, 2·7; N, 12·2, 12·35. $C_8H_6O_6N_2$ requires C, 42·5; H, 2·6; N, 12·4%).

Nitration of this compound with nitric acid (*d* 1·52) in small excess gave 5 : 6 : 8-trinitrobenzo-1 : 4-dioxan (90% yield), m. p. 180·0—180·6°, not depressed on admixture with the product obtained by nitration of the 5 : 6-dinitro-derivative (Found: N, 15·5, 15·3. Calc. for $C_8H_5O_8N_3$: N, 15·5%).

Thanks are expressed to Mr. Sie Swan Tiong for his assistance with part of this work.

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Triterpenoids. Part XXXIII. The Constitution of* cyclo*Artenol.*

By D. S. IRVINE, J. A. HENRY, and F. S. SPRING.

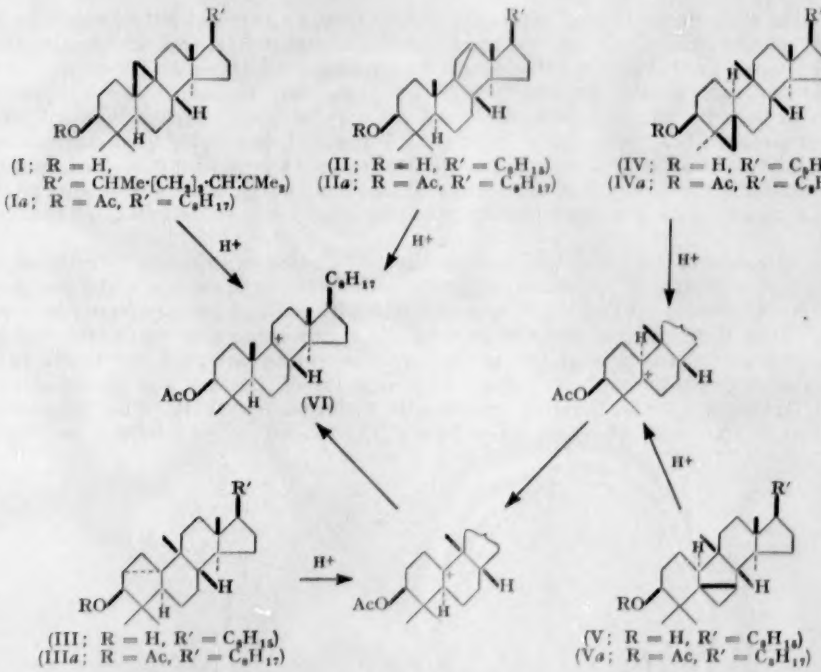
[Reprint Order No. 5973.]

*cyclo*Artenol is shown to be 9 : 19-*cyclo*lanost-24-en-3β-ol (I).

IN Part XXVIII of this Series (Bentley, Henry, Irvine, and Spring, *J.*, 1953, 3673) it was shown that *cyclo*artenol is a *cyclo*lanost-24-en-3β-ol. A limitation to the number of positions available for the *cyclo*propane ring in *cyclo*artenol was imposed by the observation that although treatment of *cyclo*artanyl acetate with hydrogen chloride gives a mixture of double-bond isomers consisting of a preponderating amount of lanost-9(11)-enyl acetate together with a smaller proportion of an equilibrium mixture of lanost-8- and lanost-7-enyl acetates, lanost-9(11)-enyl acetate is recovered unchanged after the same acid treatment and, further, that this acid treatment does not convert either the 7- or the 8-enyl acetate into lanost-9(11)-enyl acetate. Bentley *et al.* concluded that these observations prove that during the acid rearrangement of *cyclo*artanyl acetate, lanost-9(11)- and -8-enyl acetate are formed *simultaneously* by the loss of a proton from the carbonium ion (VI) and that the 8-enyl acetate subsequently equilibrates to a mixture with the 7-enyl acetate. These facts

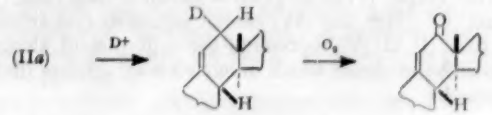
* Part XXXII, *J.*, 1955, 596.

eliminate structures from which the carbonium ion (VI) is developed by rearrangement of intermediate cations in which either $C_{(8)}$ or $C_{(11)}$ is the electron-deficient centre. Subsequently, a second limitation to the number of possible structures for *cyclo*artenol was imposed by Cole (*Chem. and Ind.*, 1953, 946; *J.*, 1954, 3810). In a valuable contribution to the chemistry of *cyclo*propane compounds, Cole showed that an infra-red absorption band at about 3042—3052 cm.$^{-1}$ is characteristic of an unsubstituted methylene group included in a *cyclo*propane ring and that such a band is present in the spectrum of *cyclo*artenol. If it is assumed that the *cyclo*propane ring in *cyclo*artenol extends from $C_{(9)}$, these considerations lead to the conclusion that the triterpenoid alcohol is either (I) or (II). When the work described in this paper was commenced, it was clear that this assumption was not justified, and that three additional formulæ (III), (IV), and (V) qualified for consideration as representing *cyclo*artenol in that each conformed to the specifications outlined above. The path to the ion (VI) by the proton-induced rearrangement of *cyclo*artanyl acetate [(I*a*), (II*a*), (III*a*), (IV*a*), or (V*a*)] is shown in each case. The experiments now described prove that (II), (III), and (IV) cannot represent *cyclo*artenol from which we conclude by negation that (I) or (V) represents the triterpenoid alcohol. However, in addition we also offer positive evidence which in our view establishes that (I) truly reflects the structure of *cyclo*artenol.


(I; R = H, R′ = CHMe·[CH$_2$]$_3$·CH:CMe$_2$)
(I*a*; R = Ac, R′ = C$_8$H$_{17}$)
(II; R = H, R′ = C$_8$H$_{17}$)
(II*a*; R = Ac, R′ = C$_8$H$_{17}$)
(IV; R = H, R′ = C$_8$H$_{17}$)
(IV*a*; R = Ac, R′ = C$_8$H$_{17}$)
(VI)
(III; R = H, R′ = C$_8$H$_{17}$)
(III*a*; R = Ac, R′ = C$_8$H$_{17}$)
(V; R = H, R′ = C$_8$H$_{17}$)
(V*a*; R = Ac, R′ = C$_8$H$_{17}$)

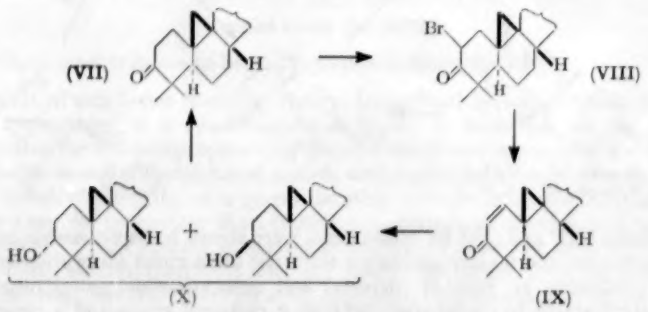
The formulæ (III) and (IV) for *cyclo*artenol were shown to be untenable on two counts. First, *cyclo*artanone and its semicarbazone show the ultra-violet absorption spectrum of a compound containing an isolated carbonyl and semicarbazone group respectively; no exaltation attributable to conjugation between a carbonyl group and a *cyclo*propane ring is observed. Secondly, *cyclo*artanone readily forms an enol acetate which shows the normal ultra-violet absorption spectrum of a simple enol acetate, *i.e.*, it does not show an exaltation attributable to conjugation between a *cyclo*propane ring and an ethylenic bond. Hydrolysis of the enol acetate regenerates *cyclo*artanone.

A method for testing the validity of structure (II) was suggested by the treatment of a similar structural problem by Barton and de Mayo (*J.*, 1953, 2178) in a study of the *cyclo*propane ring in phyllanthol. Reaction of *cyclo*artanyl acetate with deuterium chloride and a trace of deuterium oxide gave a mixture of deuterated double-bond isomers. Applying to this the partial oxidation technique successfully used for the preparation of lanost-9(11)-enyl acetate from *cyclo*artanyl acetate (Bentley *et al.*, *loc. cit.*) an *x*-deuterolanost-9(11)-enyl acetate was obtained; the m. p., rotation, and ultra-violet absorption spectrum of the deuterated compound were identical with those of lanost-9(11)-enyl acetate within the limits of experimental accuracy. Analysis of the deuterated compound showed the presence of approximately 0·8 gram-atom of deuterium per mole. If *cyclo*artenol is correctly represented by (II), the deuterated compound must be 12-deuterolanost-9(11)-enyl acetate and oxidation with chromic acid should eliminate the deuterium to yield 12-oxolanost-9(11)-enyl acetate, as follows:



Oxidation of deuterated lanost-9(11)-enyl acetate gave a compound indistinguishable in m. p., rotation, and absorption spectrum from 12-oxolanost-9(11)-enyl acetate (Bentley *et al.*, *loc. cit.*) which however still contains 0·8 gram-atom of deuterium per mole. Thus *cyclo*artenol cannot have the structure (II), and the only formulæ which adequately represent the triterpenoid alcohol are (I) and (V). At this stage, Barton, Warnhoff, and Page (*Chem. and Ind.*, 1954, 220; *J.*, 1954, 2715) reported that an infra-red examination of the mixture of isomeric deuterated lanostenes obtained by treatment of *cyclo*artane with deuterium chloride showed that the deuterated carbon atom is a deuterated methyl group other than one of the *gem*-methyl groups, and concluded that *cyclo*artenol is represented by (I).

Confirmation of this conclusion is offered in the following experiments: Treatment of *cyclo*artanone (VII) with *N*-bromosuccinimide in the presence of calcium carbonate gives 2-bromo*cyclo*artanone (VIII), which when refluxed with collidine gives *cyclo*art-1-en-3-one (IX). That these changes had not involved the *cyclo*propane ring was established by hydrogenation of the unsaturated ketone; this treatment saturated the double bond and also reduced the carbonyl group to a mixture of the 3α- and the 3β-alcohol (X). Oxidation of this mixture regenerated *cyclo*artanone (VII). The ultra-violet absorption spectrum of *cyclo*art-1-en-3-one (IX) shows a well-defined maximum



at 2690 Å which, we believe, proves that the αβ-unsaturated carbonyl group in *cyclo*art-1-en-3-one is directly conjugated with the *cyclo*propane ring. This observation eliminates the formula (V) and proves that *cyclo*art-1-en-3-one is (IX) and that *cyclo*artenol is correctly described as 9 : 19-*cyclo*lanost-24-en-3β-ol (I).

Experimental

Rotations were measured in chloroform solution at room temperature, with a 1-dm. tube, and ultra-violet absorption spectra were measured in ethanol solution with a Unicam SP. 500 spectrophotometer. Grade II alumina and a light petroleum fraction, b. p. 60—80°, were used for chromatography.

Enol Acetate of cyclo*Artanone*.—A solution of *cyclo*artanone (VII) (200 mg.) in *iso*propenyl acetate (25 ml.) containing one drop of concentrated sulphuric acid was heated on the steam-bath for 3 hr. The product, isolated by means of ether, was crystallised from chloroform–methanol to give the *enol acetate* of *cyclo*artanone as needles (160 mg.), m. p. 87°, $[\alpha]_D$ +66·5° (*c*, 1·1) (Found: C, 82·0; H, 11·5. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). The enol acetate gives a strong yellow colour with tetranitromethane. Light absorption: max. at 2060 Å (ε 1600). Hydrolysis of the enol acetate with 3% methanolic potassium hydroxide refurnished *cyclo*artanone, which separates from methanol as blades, m. p. and mixed m. p. 110°, $[\alpha]_D$ +22° (*c*, 2·0).

19-*Deuterolanost*-9(11)-*enyl Acetate*.—A solution of *cyclo*artanyl acetate (I*a*) (1 g.) in dry chloroform (30 ml.) to which two drops of deuterium oxide (99·95%) were added was shaken with deuterium chloride (prepared from phosphorus trichloride and deuterium oxide and isolated over mercury) for 36 hr. The residue obtained on removing the solvent crystallised from chloroform–methanol as plates (0·93 g.), m. p. 140—150°. A solution of this mixture in acetic acid (75 ml.) was stirred on the steam-bath, and chromic acid (0·28 g.) in 90% acetic acid added during 5 min. Heating was continued for 10 min. and the mixture diluted with water. A solution of the neutral product (0·96 g.), isolated by means of ether, in light petroleum (100 ml.) was percolated through a column (2 × 12 cm.) of alumina (30 g.). The fraction (0·45 g.) eluted by light petroleum (600 ml.) was twice crystallised from chloroform–methanol to give 19-*deuterolanost*-9(11)-*enyl acetate* as plates, m. p. 173°, $[\alpha]_D$ +84° (*c*, 1·2) [Found: C, 81·5; H + D (as H_2O), 11·7. $C_{32}H_{53}DO_2$ requires C, 81·5; H + D, 11·8%]. It shows a strong yellow colour with tetranitromethane. Mass spectrographic analysis showed the deuterium content to be 0·815 gram-atom per mole.

19-*Deutero*-12-*oxolanost*-9(11)-*enyl Acetate*.—Chromic acid (200 mg.) in acetic acid (30 ml.) was added during 1 hr. to a refluxing solution of 19-deuterolanost-9(11)-enyl acetate (200 mg.) in acetic acid (30 ml.). Heating was continued for a further 2 hr. and the mixture left overnight at room temperature. A solution of the neutral product (212 mg.) in light petroleum (25 ml.) was percolated through a column (1 × 10 cm.) of alumina (6 g.), and the fraction (130 mg.) eluted by light petroleum–benzene (1 : 1; 150 ml.) crystallised from methanol to give 19-*deutero*-12-*oxolanost*-9(11)-*enyl acetate* as needles, m. p. 183°, $[\alpha]_D$ +90° (*c*, 0·7) [Found: C, 79·4; H + D (as H_2O), 10·9. $C_{32}H_{51}DO_3$ requires C, 79·1; H + D, 11·0%]. Light absorption: max. at 2410 Å (ε 9000). Mass spectrographic analysis showed the deuterium content to be 0·811 gram-atom per mole.

2-*Bromo*cyclo*artanone* (VIII).—A solution of *cyclo*artanone (625 mg.) in carbontetra chloride (20 ml.) was refluxed for 5 min. with *N*-bromosuccinimide (314 mg., 1·2 mols.) in the presence of suspended calcium carbonate; the mixture was illuminated with a 250-w lamp. The mixture was diluted with carbon tetrachloride and filtered and the product crystallised from methanol to give a pale yellow solid (490 mg.), m. p. 100—110°. Further crystallisations from methanol gave 2-*bromo*cyclo*artanone* which separates as prismatic needles, m. p. 116°, $[\alpha]_D$ +43° (*c*, 1·2) (Found: C, 71·3; H, 9·7. $C_{30}H_{49}OBr$ requires C, 71·3; H, 9·8%).

Dehydrobromination of 2-*Bromo*cyclo*artanone*.—2-Bromo*cyclo*artanone (200 mg.) in collidine (3 ml.) was heated under reflux for 2 hr. and left overnight at room temperature, then filtered. A solution of the product, isolated by means of ether, was chromatographed on alumina (1·25 × 7·5 cm.; 6 g.). The fractions eluted by light petroleum (40 ml.) and light petroleum–benzene (4 : 1; 100 ml.) were combined and crystallised from methanol to give cyclo*art*-1-*en*-3-*one* (IX) as prisms, m. p. 100°, $[\alpha]_D$ −40° (*c*, 1·3) (Found: C, 85·0; H, 11·7. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Light absorption: maxima at 2060 (ε 5000) and at 2690 Å (ε 8700).

Reduction of cyclo*Art*-1-*en*-3-*one*.—*cyclo*Art-1-en-3-one (200 mg.) in acetic acid (125 ml.) was shaken with hydrogen and platinum (from 200 mg. of platinum oxide) for 3 hr., by which time absorption of hydrogen had ceased. The solution was filtered and evaporated and the residual gum crystallised from methanol as blades m. p. 76—87°. A solution of the crude mixture of 3α- and 3β-alcohols (X) (205 mg.) in acetic acid (125 ml.) was treated with chromic acid in acetic acid (5·85 ml., 6·4 mg./ml., 1·2 mols.) and left overnight at room temperature. The neutral product gave *cyclo*artanone which separates from methanol as blades (142 mg.), m. p. and mixed m. p. 110°, $[\alpha]_D$ +23° (*c*, 0·8) (Found: C, 84·3; H, 12·1. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%).

We thank the Department of Scientific and Industrial Research for a Maintenance Award (to D. S. I.), and the Governors of this College for the award of the Crawford and Duncan Scholarships (to J. A. H.). The deuterium microanalyses were carried out in the Division of Biochemistry of the Sloan-Kettering Institute for Cancer Research, New York, by Josephine Leong under the supervision of Drs. David K. Fukushima and T. F. Gallagher, whose collaboration is gratefully acknowledged.

THE ROYAL TECHNICAL COLLEGE, GLASGOW [*Received, December 17th*, 1954.]

The Thermal and Photochemical Decomposition of Triphenylhydrazine.

By P. F. HOLT and B. P. HUGHES.

[Reprint Order No. 5867.]

[$^{15}N_1$]Triphenylhydrazine, when decomposed by heat, gives azobenzene in which the nitrogen atoms have a random distribution. The mechanism of this decomposition is discussed. Azobenzene is also formed when triphenylhydrazine is decomposed by light and when tetraphenylhydrazine and aniline are heated in benzene solution.

TRIPHENYLHYDRAZINE in inert solvents is decomposed by heat and by light. Wieland and Reverdy (*Ber.*, 1915, **48**, 1112) refluxed triphenylhydrazine in xylene under nitrogen, and isolated diphenylamine, azobenzene, and the highly coloured benzoquinone 1-anil 4-diphenylhydrazone, $Ph_2N{\cdot}N{:}C_6H_4{:}NPh$; aniline also was detected by a colour reaction. Goldschmidt (*Ber.*, 1920, **53**, 59) decomposed triphenylhydrazine in diethyl ether by irradiation "with August sunshine." After 24 hr., he isolated from the solution diphenylamine and quinone anil diphenylhydrazone but he detected neither azobenzene nor aniline. Goldschmidt found that triphenylhydrazyl, $Ph_2N{\cdot}\dot{N}Ph$, which he produced from triphenylhydrazine solutions by the action of oxidizing agents at −55°, also gave diphenylamine and quinone anil diphenylhydrazone when heated. He proposed, therefore, a reaction mechanism for the thermal decomposition of triphenylhydrazine which involved the formation and interaction of triphenylhydrazyl radicals:

(1) $Ph_2N{\cdot}NHPh \longrightarrow Ph_2N{\cdot}\dot{N}Ph + H$

(2) $4Ph_2N{\cdot}\dot{N}Ph \longrightarrow Ph_2NH + Ph{\cdot}NH_2 + 3Ph_2N{\cdot}\dot{N}{\cdot}\dot{C}_6H_4$

(3) $Ph{\cdot}NH_2 + 2Ph_2N{\cdot}\dot{N}Ph \longrightarrow 2Ph_2N{\cdot}NHPh + PhN{:}$

(4) $Ph_2N{\cdot}\dot{N}{\cdot}\dot{C}_6H_4 + PhN{:} \longrightarrow Ph_2N{\cdot}N{:}C_6H_4{:}NPh$

Goldschmidt rejected a sequence which was inititated by reaction (1) and followed by the fission of the triphenylhydrazyl radicals into diphenylamine and phenylimine radicals:

(5) $Ph_2N{\cdot}\dot{N}Ph \longrightarrow \dot{P}h_2N{\cdot} + PhN{:}$

because he could not detect tetraphenylhydrazine among the products.

Wieland and Reverdy (*loc. cit.*) preferred a mechanism which was initiated by the transfer of a hydrogen atom and fission of the molecule to give diphenylamine and a phenylimine radical (6), the latter then dimerizing to give azobenzene (7) or reacting with triphenylhydrazine eventually to form quinone anil diphenylhydrazone (8) and (9):

(6) $Ph_2N{\cdot}NHPh \longrightarrow Ph_2NH + PhN{:}$

(7) $2PhN{:} \longrightarrow PhN{:}NPh$

(8) $Ph_2N{\cdot}NHPh + PhN{:} \longrightarrow Ph_2N{\cdot}NH{\cdot}C_6H_4{\cdot}NHPh$

(9) $Ph_2N{\cdot}NH{\cdot}C_6H_4{\cdot}NHPh \longrightarrow Ph_2N{\cdot}N{:}C_6H_4{:}NPh + 2H$

The hydrogen atoms reduce triphenylhydrazine to diphenylamine and aniline:

(10) $Ph_2N{\cdot}NHPh + 2H \longrightarrow Ph_2NH + Ph{\cdot}NH_2$

This mechanism is not, however, applicable to the oxidation of triphenylhydrazine in which the initial stage must involve the removal of hydrogen and the production of triphenylhydrazyl radicals.

Another mechanism can be postulated which is an extension of that proposed by Dewar (unpublished; reported by Swarc, *Chem. Rev.*, 1950, **47**, 151) for the thermal decomposition of hydrazobenzene, by assuming that the triphenylhydrazine first splits into a phenylamine radical and a diphenylamine radical (11). Azobenzene might then be formed by attack of a phenylamine radical on a molecule of triphenylhydrazine (12) and subsequent loss of hydrogen by the diphenylhydrazyl so formed (13):

$$\text{(11)} \quad Ph_2N{\cdot}NHPh \longrightarrow Ph_2N\cdot + Ph{\cdot}\dot{N}H$$

$$\text{(12)} \quad Ph{\cdot}\dot{N}H + Ph_2N{\cdot}NHPh \longrightarrow Ph_2NH + Ph\dot{N}{\cdot}NHPh$$

$$\text{(13)} \quad Ph\dot{N}{\cdot}NHPh \longrightarrow PhNN{:}Ph + H$$

We have sought fresh evidence concerning the mechanism of the decomposition of triphenylhydrazine by applying new methods for the separation of reaction products and by studying the azobenzene which is formed by the decomposition of isotopically labelled triphenylhydrazine.

Some information about the mechanism by which azobenzene is formed from triphenylhydrazine can be obtained by decomposing triphenylhydrazine which has been isotopically labelled at one nitrogen atom. This technique has been applied already to the decomposition of hydrazobenzene (Holt and Hughes, *J.*, 1953, 1666; 1955, 98). If the azo-group of a molecule of azobenzene is derived solely from one molecule of [$^{15}N_1$]triphenylhydrazine, then the distribution of the nitrogen isotopes in the azobenzene will be non-random, but if the azobenzene is formed from fragments containing only one nitrogen atom, the distribution of the nitrogen isotopes in the azobenzene will be random.

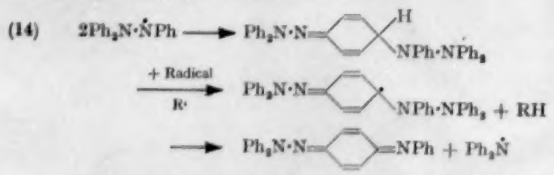
The results of mass-spectrometric measurements on nitrogen samples derived from the azobenzene are expressed as the ratio of the masses (R) $(^{14}N{\cdot}^{15}N)^2/(^{14}N{\cdot}^{14}N)(^{15}N{\cdot}^{15}N)$ which ratio, if random distribution exists, has the theoretical value 4. The results of two experiments gave values for R of 4·3 and 4·2, indicating random pairing. This result differs from that obtained when [$^{15}N_1$]hydrazobenzene is decomposed photochemically or thermally to give azobenzene, as then random pairing does not occur. The mechanism which is denoted by equations (11)—(13) is not, therefore, applicable. The slight deviations from 4 of the experimental values of R are doubtless due to traces of hydrazobenzene which is also formed in the preparative reaction.

A repetition of Wieland and Reverdy's work (*loc. cit.*) confirmed that the main products of the thermal decomposition of triphenylhydrazine are azobenzene and diphenylamine. Aniline is also formed and can be detected by colour tests but in amount insufficient for isolation. The products are the same whether the decomposition is carried out in xylene, benzene, or ethanol.

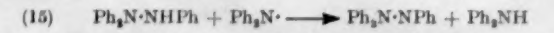
Irradiation of an ethereal solution of triphenylhydrazine by ultraviolet light was found to produce diphenylhydrazine and quinone anil diphenylhydrazone, but no aniline. This result confirms Goldschmidt's report. However, contrary to Goldschmidt's findings, it was possible to isolate also a quantity of azobenzene by using chromatography. A known amount of triphenylamine was irradiated and the material was isolated and weighed so that the amount which had been decomposed could be deduced. It was apparent that thermal decomposition of triphenylhydrazine gives approximately twice as much azobenzene as does the photochemical reaction. Goldschmidt's observation that azobenzene is not formed when triphenylhydrazine is oxidized by lead dioxide was confirmed.

Goldschmidt considered that the thermal and the photochemical decomposition and the oxidation of triphenylhydrazine at normal temperatures were analogous, stating that the formation of azobenzene in the thermal reaction was due to the elevated temperature. His argument is no longer sound since azobenzene is also formed photochemically. Moreover, the ter- and the quadri-molecular reaction involved make the reaction mechanism proposed by Goldschmidt improbable.

The decomposition of triphenylhydrazyl can be explained without recourse to quadrimolecular reactions by the following scheme : *

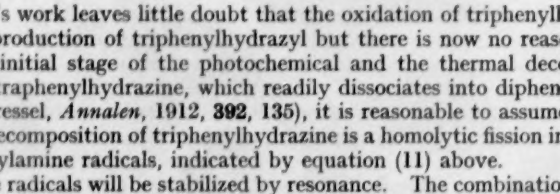


Initially the radical R· in this reaction will be triphenylhydrazyl but subsequently diphenylamine radicals also. The diphenylamine radical which is produced is removed according to equation (15) :

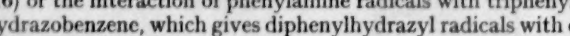


Goldschmidt's work leaves little doubt that the oxidation of triphenylhydrazine results initially in the production of triphenylhydrazyl but there is now no reason to retain this reaction as the initial stage of the photochemical and the thermal decomposition. By analogy with tetraphenylhydrazine, which readily dissociates into diphenylamine radicals (Wieland and Fressel, *Annalen*, 1912, **392**, 135), it is reasonable to assume that the initial reaction in the decomposition of triphenylhydrazine is a homolytic fission into the diphenylamine and phenylamine radicals, indicated by equation (11) above.

Both of these radicals will be stabilized by resonance. The combination of two phenylamine radicals (16) or the interaction of phenylamine radicals with triphenylhydrazine (17), would produce hydrazobenzene, which gives diphenylhydrazyl radicals with either diphenylamine radicals or phenylamine radicals.



The diphenylhydrazyl radicals may react with diphenylamine radicals to give azobenzene (20) :



The diphenylamine and phenylamine radicals may in a similar way remove hydrogen atoms from triphenylhydrazine with the eventual formation of quinone anil diphenylhydrazone as described earlier in equation (14).

The absence of aniline in the photochemical reaction and the presence of only a trace in the thermal reaction may mean only that the aniline is removed by interaction with another free radical to give phenylamine radicals (21) which then take part in reaction (16) or (17) :

The feasibility of this mechanism was demonstrated by studying the action of diphenylamine radicals produced by the dissociation of tetraphenylhydrazine. When heated in benzene solution under nitrogen, tetraphenylhydrazine and aniline give azobenzene, a product which is most likely to be formed by the reaction (21) followed by reactions (16)—(20).

Experimental

[$^{15}N_2$]*Triphenylhydrazine.*—The method described by Holt and Hughes (*J.*, 1954, **764**) for for the preparation of unlabelled material was used. [$^{15}N_2$]Azobenzene (500 mg.) (Holt and Hughes, *J.*, 1953, **1666**) was dissolved in dry ether (20 ml.) under nitrogen and cooled to 0°. To

* We thank a Referee for suggesting the alternative mechanism incorporated in equation (14).

this, a solution of phenyl-lithium (230 mg.) in dry ether (5 ml.) was added. The mixture was stirred for 5 min., then saturated ammonium chloride was added. The residue left on evaporation of the ethereal layer, when washed with light petroleum and recrystallized from ethanol, gave [$^{15}N_1$]triphenylhydrazine, m. p. 141—142° (decomp.) (100 mg.).

Thermal Decomposition of [$^{15}N_1$]*Triphenylhydrazine.*—[$^{15}N_1$]Triphenylhydrazine (100 mg.) in benzene (5 ml.), in a Pyrex tube, was frozen in solid carbon dioxide and evacuated; the tube was sealed, heated for 2 hr. at 140° ± 1°, then cooled and opened. The contents were evaporated to dryness in a vacuum. The residue was dissolved in light petroleum (b. p. 40—60°), and the azobenzene (12—13 mg.) was separated by chromatography on alumina and eluted with light petroleum; it had m. p. 67—68°.

Nitrogen samples were derived from the $^{15}N_1$-azobenzene by the combustion procedure described by Holt and Hughes (*J.*, 1955, 95).

Thermal Decomposition of Unlabelled Triphenylhydrazine.—Unlabelled triphenylhydrazine (100 mg.) was similarly decomposed with a view to examining the other products of the reaction. By steam-distillation diphenylamine and the azobenzene were separated. The distillate was slightly acidified, then extracted with ether. Dry hydrogen chloride was passed through the dried ethereal solution, which contained the diphenylamine and azobenzene, and the precipitated diphenylamine hydrochloride was separated by filtration. Diphenylamine (m. p. 53—54°; 38 mg.) was obtained when the hydrochloride was washed with dilute ammonia. The quinone anil diphenylhydrazone is destroyed by steam-distillation and was not isolated.

Photochemical Decomposition of Triphenylhydrazine.—Triphenylhydrazine (100 mg.) in dry ether (25 ml.) under nitrogen was irradiated in a Pyrex tube with a low-pressure mercury-arc lamp (Thermal Syndicate Ltd., Type T/M5/564/0) for 24 hr. The reaction vessel and arc tube were housed in a Dewar flask. To cool the apparatus, the flask was filled with water which was constantly changed. Azobenzene (2—3 mg.; m. p. 67°) was separated as described above. The unchanged triphenylhydrazine (47 mg.) was also isolated by chromatography.

Oxidation of Triphenylhydrazine.—Triphenylhydrazine (100 mg.) in dry ether (10 ml.) was shaken with lead dioxide (1 g.) for 1 hr. The solution was filtered and the residue was washed with ether (10 ml.). The combined filtrate and washings were evaporated *in vacuo* and the residue was redissolved in light petroleum (b. p. 40—60°). The ethereal solution was adsorbed on alumina and eluted with more ether. No azobenzene was detected. Tests showed that 0·5 mg. of azobenzene could be detected by this procedure.

Reaction of Aniline with Tetraphenylhydrazine.—Tetraphenylhydrazine (1 g.) (Wieland and Gambarjan, *Ber.*, 1906, **39**, 1500) was dissolved in benzene (30 ml.) under nitrogen, and freshly distilled aniline (0·2 g.) was added. The solution was refluxed for 2 hr. Azobenzene (m. p. and mixed m. p. 68°; lit., 68°) and diphenylamine (m. p. and mixed m. p. 54°; lit., 54°) were isolated by chromatography on alumina.

We are indebted to Dr. D. H. Tomlin who assayed our nitrogen samples, and to Imperial Chemical Industries Limited, Paints Division, for a grant to one of us (B. P. H.).

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*The Chemistry of Ribose and its Derivatives. Part IV.**
2 : 3-*Di*-O-*methyl*-D-*ribose.*

By G. R. BARKER and D. C. C. SMITH.

[Reprint Order No. 5931.]

The synthesis and characterisation of 2 : 3-di-*O*-methyl-D-ribose are described.

IN Part II (Barker and Lock, *J.*, 1950, 23) methylated di-D-ribofuranose-1 : 5′-5 : 1′-dianhydride was shown to yield, on hydrolysis, 2 : 3-di-*O*-methyl-D-ribose. However, no crystalline derivatives were obtained and the structure of the sugar was assigned on the basis of evidence derived only from periodate oxidations. The behaviour of 2 : 3-di-*O*-methyl-D-ribose on paper chromatography and ionophoresis in presence of borate has

* Part III, *J.*, 1954, 2151.

been described (Brown, Magrath, and Todd, *J.*, 1954, 1444), but the synthesis and characterisation of the sugar were not recorded. It was therefore desirable to confirm the structure of this sugar and this has now been undertaken as part of a study of all the methyl ethers of D-ribose.

Various compounds have been described in which the hydroxyl group at $C_{(5)}$ of ribose is blocked by the triphenylmethyl (trityl) group, and it was decided to attempt the synthesis of 2 : 3-di-*O*-methyl-D-ribose by use of a trityl derivative of the sugar. Tritylation of methyl D-ribofuranoside yielded amorphous methyl 5-*O*-trityl-D-ribofuranoside which was methylated with methyl iodide and silver oxide to syrupy methyl 2 : 3-di-*O*-methyl-5-*O*-trityl-D-ribofuranoside. Removal of the trityl group by hydrogenolysis with a palladium–charcoal catalyst was slow and incomplete; however, some methyl 2 : 3-di-*O*-methyl-D-ribofuranoside was obtained. Detritylation with hydrogen chloride in chloroform was more convenient and yielded a mixture of 2 : 3-di-*O*-methyl-D-ribose and its methyl glycoside, which was converted into methyl 2 : 3-di-*O*-methyl-D-ribopyranoside by boiling methanolic hydrogen chloride. Hydrolysis of this material gave 2 : 3-di-*O*-methyl-D-ribose. Since trityl chloride is known to react preferentially with primary alcoholic groups (Helferich, *Adv. Carbohydrate Chem.*, 1948, **3**, 79), the structure of the dimethyl ribose obtained could be deduced with some degree of certainty from the method of synthesis. In order to confirm the correctness of the allocation of the methyl groups, the sugar was oxidised to a crystalline lactone, which was hydrolysed at a rate characteristic of γ-lactones. This indicates that the hydroxyl group at $C_{(4)}$ is unsubstituted. Furthermore, the methylated sugar yielded a crystalline phenylosazone with loss of one methoxyl group. This behaviour is characteristic of sugars bearing a methoxyl group at $C_{(2)}$. The only two structures possible for the sugar are, therefore, 2 : 3- and 2 : 5-di-*O*-methyl-D-ribose. In order to exclude the latter, the sugar was converted into a pyranose glycoside. Two distinct glycosides were obtained by treatment of the presumed 2 : 3-di-*O*-methyl-D-ribose with methanolic hydrogen chloride, respectively, at room temperature and at the boiling point. The former was hydrolysed by 0·2N-sulphuric acid at 95—100° at a rate characteristic of furanosides. The hydrolysis of the other glycoside was rapid in the initial stages, and slower in the later stages. This suggested that the material consisted of a pyranoside contaminated with some furanoside. Methylation of the mixed glycosides with methyl sulphate and sodium hydroxide, and hydrolysis of the product yielded a syrup which was shown by paper chromatography to consist of 2 : 3 : 4-tri-*O*-methyl-D-ribose together with a small quantity of 2 : 3 : 5-tri-*O*-methyl-D-ribose. The syrup partially crystallised when kept and the solid, after purification, was identical with authentic 2 : 3 : 4-tri-*O*-methyl-D-ribose. This trimethylribose must of necessity have been formed from a pyranose glycoside of the dimethylribose which is therefore 2 : 3-di-*O*-methyl-D-ribose.

The 2 : 3-di-*O*-methyl-D-ribose obtained from di-D-ribose-1 : 5′-1′ : 5-dianhydride (Barker and Lock, *loc. cit.*) consumed one mol. of sodium metaperiodate and gave no formic acid. However, although the amount of oxidant used was that expected on the basis of oxidation in the open-chain form, the theoretical quantity of formaldehyde could not be recovered. In view of the fact that certain sugars are now known to be oxidised by sodium metaperiodate in a lactol form (Barker and Smith, *Chem. and Ind.*, 1952, 1035), 2 : 3-di-*O*-methyl-D-ribose was investigated further. The sugar consumed one mol. of sodium metaperiodate with the production of a negligible quantity of titratable acid, and approximately one mol. of formaldehyde was isolated as its dimedone complex. The low yield of formaldehyde obtained in the previous experiments was apparently due to the fact that the oxidation was of necessity carried out on a small scale resulting in incomplete precipitation of the dimedone complex. It is concluded that the sugar from the ribose anhydride was correctly identified and that 2 : 3-di-*O*-methyl-D-ribose behaves as an aldehydo-sugar towards periodate.

Experimental

M.p.s were determined on a Kofler block.

Methyl 5-O-Trityl-αβ-D-ribofuranoside.—Methyl αβ-D-ribofuranoside (Barker, *J.*, 1948, 2035) (5·4 g.) and triphenylchloromethane (9·9 g.) in dry pyridine (100 c.c.) were shaken until

dissolved, and after 7 days at 15° poured into water (1·5 l.). The precipitated gum was dissolved in chloroform, washed three times with ice-cold 5% aqueous sodium hydrogen sulphate, once with water, and once with sodium hydrogen carbonate solution, and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded the *product* as a fluffed glass (12·1 g.) (Found: OMe, 7·4; $OCPh_3$, 63·1. $C_{25}H_{26}O_5$ requires OMe, 7·6; $OCPh_3$, 63·9%).

Methyl 2 : 3-*Di*-O-*methyl*-5-O-*trityl*-αβ-D-*ribofuranoside*.—Methyl 5-*O*-trityl-αβ-D-ribofuranoside (11·9 g.) in methyl iodide (35 c.c.) was boiled under reflux with vigorous stirring, and silver oxide (32 g.) was added in four portions at intervals of 15 min. The mixture was refluxed for 1 hr. longer, and then filtered, and the treatment was repeated a further three times. After the final filtration, the solvent was removed under reduced pressure yielding a syrupy *glycoside* (11·4 g., 90%) which was purified by molecular distillation (Found: OMe, 21·5. $C_{27}H_{30}O_5$ requires OMe, 21·4%).

Methyl 2 : 3-*Di*-O-*methyl*-αβ-D-*ribopyranoside*.—A solution of methyl 2 : 3-di-*O*-methyl-5-*O*-trityl-αβ-D-ribofuranoside (11·2 g.) in chloroform (250 c.c.) was saturated with hydrogen chloride at 0°, and kept at this temperature for 2 hr. Chloroform and hydrogen chloride were removed under reduced pressure, and the residue triturated with water. Triphenylmethanol (6·8 g.) was filtered off, and the filtrate was titrated to pH 7 with N-sodium hydroxide, evaporated to dryness, and extracted with methanol. The syrup (3·9 g.) obtained after removal of solvent was boiled with 2% methanolic hydrogen chloride (75 c.c.) for 7 hr. Chloride ions were removed by grinding with silver oxide and filtration through charcoal, and the filtrate was evaporated. The *product* (3·3 g.) had b. p. 130° (bath temp.)/0·01 mm., n_D^{19} 1·4557 (Found: C, 50·5; H, 8·7. $C_8H_{16}O_5$ requires C, 50·0; H, 8·3%).

2 : 3-*Di*-O-*methyl*-D-*ribose*.—Methyl 2 : 3-di-*O*-methyl-αβ-D-ribopyranoside (0·51 g.) in 0·2N-sulphuric acid (5 c.c.) was heated at 95—100° to constant rotation, passed through Amberlite IR-4B(OH), evaporated, and distilled in the molecular still to give 2 : 3-*di*-O-*methyl*-D-*ribose* as a viscous syrup, $[\alpha]_D^{17}$ −16·6° (*c*, 6·48 in H_2O), n_D^{16} 1·4750 (Found: C, 47·2; H, 7·8; OMe, 32·2. $C_7H_{14}O_5$ requires C, 47·2; H, 7·9; OMe, 34·8%). It yielded a *toluene*-p-*sulphonylhydrazone*, m. p. 139—140° (Found: C, 48·8; H, 6·7; N, 8·4; OMe, 18·4. $C_{14}H_{22}O_7N_2S$ requires C, 48·5; H, 6·4; N, 8·1; OMe, 17·9%).

3-O-*Methyl*-D-*ribose Phenylosazone*.—2 : 3-Di-*O*-methyl-D-ribose (72 mg.), phenylhydrazine (175 mg.), acetic acid (170 mg.), and water (5 c.c.) were heated at 80° for 5 hr. and evaporated to dryness *in vacuo*, and the residue, in the minimum of ether, chromatographed on a column (diameter 2·8 cm.) of alumina [Spence, grade H (80 g.), deactivated by shaking in ether with water (12 c.c.) and acetic acid (0·4 c.c.)]. The yellow phenylosazone band was collected, the solvent evaporated, and the residue taken up in boiling methanol (2 c.c.) and precipitated by addition of water till just turbid and cooled, giving amorphous yellow flocks (22 mg.), m. p. 135—140° (Found: C, 62·1; H, 6·7; N, 14·6; OMe, 8·2. $C_{18}H_{22}O_3N_4$ requires C, 63·1; H, 6·5; N, 16·4; OMe, 9·1%).

Methyl 2 : 3-*Di*-O-*methyl*-αβ-D-*ribofuranoside*.—(*a*) Methyl 2 : 3-di-*O*-methyl-5-*O*-trityl-αβ-D-ribofuranoside (11·4 g.) was hydrogenated at approximately atmospheric pressure in presence of a palladium–charcoal catalyst (0·7 g.; 12% Pd). When uptake of hydrogen became slow, the mixture was shaken with air for 10 min., and shaking with hydrogen was then resumed. This procedure was repeated six times. The grey solid, containing the catalyst, was removed by filtration. Extraction of the solid with hot benzene and removal of the solvent gave bistriphenylmethyl peroxide, m. p. 188° (decomp.) (Found: C, 87·4; H, 5·9. Calc. for $C_{38}H_{30}O_3$: C, 88·0; H, 5·8%). The filtrate from the catalyst was concentrated to dryness. Crystals of triphenylmethane which appeared during the distillation were collected and after crystallisation from methanol had m. p. 90°. The residue was taken up in a mixture of benzene (50 c.c.) and water (50 c.c.), and the aqueous layer after evaporation under reduced pressure yielded *methyl* 2 : 3-*di*-O-*methyl*-αβ-D-*ribofuranoside* as a mobile syrup (1·3 g.), b. p. 110° (bath temp.)/0·01 mm., n_D^{22} 1·4554 (Found: OMe, 46·0. $C_8H_{16}O_5$ requires OMe, 48·4%).

(*b*) A solution of 2 : 3-di-*O*-methyl-D-ribose (0·378 g.) in 1% methanolic hydrogen chloride (30 c.c.) was kept at 25° for 50 min. The solution was neutralised with silver oxide, filtered through "Norit," and evaporated to a syrup. This was used immediately for the following experiments since it is very hygroscopic and slowly underwent slight hydrolysis.

Hydrolysis of Methyl 2 : 3-*Di*-O-*methyl*-αβ-D-*ribofuranside and Methyl* 2 : 3-*Di*-O-*methyl*-αβ-D-*ribopyranoside*.—Each riboside was hydrolysed at 95—100°, and the reactions followed polarimetrically. The furanoside (378 mg.) in 0·2N-sulphuric acid (3 c.c.) had α_D (1 dm.) +1·29° (initial), −0·73° (10 min.), −1·26° (20 min.), −1·43° (30 min.), −1·56° (40 min.), −1·61° (50 min.), −1·62° (60 min.). The pyranoside (512 mg.) in 0·2N-sulphuric acid (5 c.c.) had α_D

(1 dm.) −2·12° (initial), −2·55° (10 min.), −2·61° (20 min.), −2·63° (30 min.), −2·61° (40 min.), −2·56° (50 min.), −2·44° (70 min.), −2·25° (98 min.), −1·74° (208 min.), −1·25° (368 min.), −1·02° (538 min.), −0·81° (778 min.).

2 : 3-*Di*-O-*methyl*-D-*ribonolactone*.—Methyl 2 : 3-di-*O*-methyl-αβ-D-ribopyranoside (0·862 g.) was hydrolysed in N-sulphuric acid (5 c.c. at 95—100° for 7 hr.), and the cooled solution was passed through Amberlite IR-4B(OH) to remove sulphuric acid. The eluate was evaporated to 20 c.c., mixed with bromine (1 c.c.), and kept in a stoppered flask at room temperature for 4 days. Excess of bromine was removed by aeration, bromide ions were removed by grinding with silver oxide, and silver ions were removed from the filtrate with hydrogen sulphide. The filtrate after removal of silver sulphide was evaporated to a syrup which crystallised (0·758 g.). This was sublimed in a high vacuum (yield 0·670 g.). The *lactone* was then recrystallised by dissolving it in warm ethyl acetate (6 parts), adding ether (6 parts), and cooling. It was obtained as flat prisms, m. p. 77·5°, $[\alpha]_D^{19}$ −31·5° (initial value), −29·6° (38 min.), −24·4° (95 min.), −19·3° (180 min.), −16·0° (278 min.), −14·3° (381 min.) (*c*, 17·39 in H_2O) (Found : C, 47·6; H, 6·9; OMe, 35·5. $C_7H_{12}O_5$ requires C, 47·7; H, 6·9; OMe, 35·6%). By dissolving the lactone in the equivalent amount of N-sodium hydroxide, warming the solution to 80° for 20 min., cooling it, and adding the exact equivalent of N-hydrochloric acid, a solution of 2 : 3-di-*O*-methyl-D-ribonic acid was obtained, having $[\alpha]_D^{20}$ +36·1° (initial value ; *c*, 5·80 in 0·5N-sodium chloride).

Periodate Oxidation of 2 : 3-*Di*-O-*methyl*-D-*ribose*.—A solution of 2 : 3-di-*O*-methyl-D-ribose (170·3 mg.) in 0·294M-sodium metaperiodate (5·0 c.c.) was kept at room temperature. Excess of periodate was determined by Barneby's method (*J. Amer. Chem. Soc.*, 1916, **38**, 330), formaldehyde by Reeves's method (*ibid.*, 1941, **63**, 1476), and free acid by titrating samples with 0·01N-sodium hydroxide to the end-point of screened methyl red, after reduction of the excess of periodate with ethylene glycol. After 6·5 hr. 1·01 mol. of periodate had been consumed, 0·95 mol. of formaldehyde was recovered and 0·08 equivalent of acid was titrated.

Methylation of Methyl 2 : 3-*Di*-O-*methyl*-αβ-D-*ribopyranoside*.—The compound (1·0 g.) in 40% aqueous sodium hydroxide (15 c.c.) was stirred in an atmosphere of nitrogen at 60°, and methyl sulphate (6·9 c.c.) was added continuously during 5 hr. Stirring was continued for 2 hr., then at 100° for 20 min. The mixture was filtered, diluted to 50 c.c., and extracted with chloroform. The extract was neutralised and dried ($MgSO_4$), and on evaporation yielded a syrup (0·88 g.), b. p. 100° (bath temp.)/15 mm., n_D^{20} 1·4451 (Found : OMe, 59·0. Calc. for $C_9H_{18}O_4$: OMe, 60·2%). The riboside (0·25 g.) was hydrolysed in N-hydrochloric acid at 95—100° to constant rotation (3 hr.), and the solution neutralised with silver carbonate, filtered through " Norit," and evaporated to a syrup (0·08 g.). Paper chromatography in *n*-butanol–water showed two spots : a stronger one, R_F 0·62, corresponding to authentic 2 : 3 : 4-tri-*O*-methyl D-ribose, and a weaker one, R_F 0·65, corresponding to authentic 2 : 3 : 5-tri-*O*-methyl-D-ribose. Repeated recrystallisation of the partly crystalline syrup from ether–light petroleum (b. p. 30—40°) gave 2 : 3 : 4-tri-*O*-methyl-D-ribopyranose (13 mg.), m. p. 88·5—91° (Found : C, 49·9; H, 8·4. Calc. for $C_8H_{16}O_5$: C, 50·0; H, 8·3%). It yielded an *anilide* as needles [from light petroleum (b. p. 40—60°)], m. p. 57·5—58·5° (Found : C, 64·2; H, 8·9; N, 6·0. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9; N, 5·2%).

3 : 4-*Di*-O-*methyl*-D-*ribose Phenylosazone*.—2 : 3 : 4-Tri-*O*-methyl-D-ribose (94 mg.), phenylhydrazine (253 mg.), acetic acid (260 mg.), and water (4 c.c.), were heated at 95—100° for 2 hr., and the mixture evaporated to dryness, and chromatographed as described above. After being rechromatographed twice, the *phenylosazone* was obtained from methanol–water as yellow amorphous flocks, m. p. 141° after softening at 135—140° and crystallising as needles at 140° (Found : C, 63·0; H, 7·0; N, 16·7; OMe, 15·0. $C_{19}H_{24}O_3N_4$ requires C, 64·0; H, 7·0; N, 15·7; OMe, 17·5%).

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The Chemistry of Ribose and Its Derivatives. Part V. The Synthesis of Methyl Ethers by Partial Methylation.*

By G. R. Barker, T. M. Noone, D. C. C. Smith, and J. W. Spoors.

[Reprint Order No. 5932.]

By methods involving partial methylation, 2- and 3-*O*-methyl-D-ribose, and 2 : 5- and 3 : 5-di-*O*-methyl-D-ribose have been synthesised and characterised. The chromatographic behaviour of 4-*O*-methyl-D-ribose is also described.

Of the methyl ethers of ribose, 5-*O*-methyl-D-ribose (Levene and Stiller, *J. Biol. Chem.*, 1934, **102**, 187), 2 : 3-di-*O*-methyl-D-ribose (Barker and Smith, preceding paper), 2 : 3 : 5-tri-*O*-methyl-D-ribose (Barker, *J.*, 1948, 2035), and 2 : 3 : 4-tri-*O*-methyl-D-ribose (Levene and Tipson, *J. Biol. Chem.*, 1931, **93**, 623) have been fully characterised. As far as is known, no unambiguous route is available for the synthesis of other methyl ethers of this sugar. Since methylated riboses are obtained from methylated nucleotides and polynucleotides it is particularly desirable that 2- and 3-*O*-methyl-D-riqose, and 2 : 5- and 3 : 5-di-*O*-methyl-D-ribose should be available synthetically. Attempts have therefore been made to obtain these ethers of ribose by partial methyation and to develop techniques for their isolation from the mixtures so produced. Part of this work has already been briefly summarised (Barker and Smith, *Chem. and Ind.*, 1954, 19).

Brief treatment of methyl 5-*O*-trityl-D-ribofuranoside with methyl iodide and silver oxide gave, after removal of protective groups, a mixture which on paper chromatograms in a butanol–water system showed three spots corresponding to D-ribose, 2 : 3-di-*O*-methyl-D-ribose, and a mono-*O*-methyl-D-ribose fraction. On a preparative scale it was subsequently found more convenient to isolate the monomethylribose fraction by chromatography on neutral alumina before removal of the protecting groups. The mixed monomethylriboses were percolated through Dowex-1 ion-exchanger in the borate form (cf. Khym and Zill, *J. Amer. Chem. Soc.*, 1952, **74**, 2099). Elution with 0·01M-sodium tetraborate gave two fractions which were freed from sodium ions and concentrated to small volume. Chromatography of these two fractions on paper, with butanol–water, gave two distinct spots, the slower of which (component *A*) had the same R_F value as that previously observed for the whole mono-*O*-methylribose fraction. The faster-moving spot (component *B*) appeared to be contaminated with non-carbohydrate material since it had a concave rear boundary. By running chromatograms of boric acid alone, and by using the spray reagent of Buchanan, Dekker, and Long (*J.*, 1950, 3162), it was found that a spot probably containing boric acid was present between the two carbohydrate spots. It was then found that chromatography of the original mono-*O*-methyl-D-ribose fraction on paper impregnated with boric acid (cf. Rose and Sweigert, *J. Amer. Chem. Soc.*, 1951, **73**, 5903) also gave two spots corresponding to those given by the fractions obtained by ion-exchange chromatography. In this way, interference by local concentrations of boric acid was avoided. The two spots were believed to correspond to 2- and 3-*O*-methyl-D-ribose and in order to determine which spot corresponded to which isomer, the following series of experiments was undertaken.

Condensation of methyl D-ribopyranoside with acetone gave a syrupy methyl *iso*propylidene-D-riboside. Levene and Stiller (*J. Biol. Chem.*, 1934, **106**, 421) have shown that during this condensation a partial change in the size of the sugar ring takes place, and they considered that the product contained methyl 2 : 3-*O*-*iso*propylidene-D-ribofuranoside and methyl 2 : 3-*iso*propylidene-D-ribopyranoside. However, no evidence for the structure of the latter was provided and it appeared to us that methyl 3 : 4-*O*-*iso*propylidene-D-ribopyranoside might also be present. After methylation of the mixed product and removal of protecting groups, chromatography on Dowex-1 borate gave two fractions. Paper chromatography of fraction 2 in butanol–boric acid indicated that

* Part IV, preceding paper.

it was identical with component *A* obtained from methyl 5-*O*-trityl-D-ribofuranoside. Under the same conditions fraction 1 was resolved into two spots, one having the same R_F value as 5-*O*-methyl-D-ribose, the other having an R_F value different from any of those of methyl ethers of ribose so far encountered. Provided that acetone condenses only with adjacent hydroxyl groups, the only methylriboses which could arise from the mixed methyl *iso*propylidene-D-ribosides are 2-, 4-, and 5-*O*-methyl-D-ribose. On the other hand, methyl 5-*O*-trityl-D-ribofuranoside can give only 2- and 3-*O*-methyl-D-ribose. Thus 2-*O*-methyl-D-ribose is expected to be formed by both routes. From the chromatographic evidence, we therefore associate this compound with component *A* and fraction 2. Component *B* is thus tentatively identified as 3-*O*-methyl-D-ribose, and fraction 1 appears to consist of 5- and 4-*O*-methyl-D-ribose. This last compound was not studied further, but from the results now reported, it appears that not only is some methyl 2 : 3-*O*-isopropylidene-D-ribofuranoside formed in the condensation of acetone with methyl D-ribopyranoside, as suggested by Levene and Stiller (*loc. cit.*), but both methyl 2 : 3- and methyl 3 : 4-*O*-*iso*propylidene-D-ribopyranoside. This reaction is being studied further.

2- and 3-*O*-Methyl-D-ribose obtained by elution of appropriate portions of paper chromatograms were purified by conversion into the methyl furanosides which were sublimed *in vacuo* and reconverted into the free sugars. The material previously identified as 2-*O*-methyl-D-ribose gave D-ribose phenylosazone, with loss of methoxyl, and consumed two mols. of sodium metaperiodate and liberated one mol. of titratable acid. The material previously identified as 3-*O*-methyl-D-ribose gave an osazone identical with that derived from 2 : 3-di-*O*-methyl-D-ribose (Barker and Smith, preceding paper). The progress of the oxidation of this sugar with sodium metaperiodate was more complex than in the above case, but nevertheless consistent with its formulation as 3-*O*-methyl-D-ribose. It rapidly consumed 1 mol. of periodate with the liberation of no titratable acid, but thereafter slowly liberated 1 mol. of acid and consumed a further mol. of periodate. It is believed that this behaviour is due to the sugar's reacting initially with the periodate in one of its lactol forms (cf. Barker and Smith, *Chem. and Ind.*, 1952, 1035). The chromatographic identifications of 2- and 3-*O*-methyl-D-ribose are thus confirmed. It may also be pointed out that it is now possible to identify chromatographically all the monomethyl ethers of ribose, by use of a combination of the procedures outlined above. With these techniques, it was shown that methylation of benzylideneguanosine yielded, after hydrolysis, 5-*O*-methyl-D-ribose as the sole methylated sugar, thus confirming the conclusion of Brown, Haynes, and Todd (*J.*, 1950, 643). The same result was also obtained with the condensation product of benzaldehyde and methyl D-ribofuranoside, showing that condensation takes place with adjacent hydroxyl groups in this case also. This is to be expected since, whereas in methyl D-glucopyranoside, which condenses with benzaldehyde at the 4- and the 6-position, the $C_{(5)}$–$C_{(6)}$ and $C_{(4)}$–$O_{(4)}$ bonds can assume equatorial positions, this is not so in the case of ribofuranoside derivatives. This probably results in the oxygen atoms at the 3- and the 5-position being too far apart for condensation (cf. condensation products of xylose and acetone; Haworth and Porter, *J.*, 1928, 611). It is of interest to observe that the condensation product of benzaldehyde and methyl β-D-ribopyranoside, after methylation and hydrolysis, gave only 5-*O*-methyl-D-ribose. It is evident that in this condensation complete change of the size of the ring takes place instead of a partial change as observed by Levene and Stiller (*loc. cit.*) in the condensation with acetone.

The successful synthesis of 2- and 3-*O*-methyl-D-ribose suggested a similar route to 2 : 5- and 3 : 5-di-*O*-methyl-D-ribose from 5-*O*-methyl-D-ribose. Levene and Stiller (*J. Biol. Chem.*, 1932, **102**, 187) obtained 5-*O*-methyl-D-ribose by methylation of methyl 2 : 3-*O*-*iso*propylidene-D-ribofuranose. Since there is a possibility of partial change of ring size in this case also, it was necessary to modify the preparation of 5-*O*-methyl-D-ribose and the preparation and characterisation of a homogeneous material are described in the experimental section.

Methyl 5-*O*-methyl-D-ribofuranoside was methylated with methyl iodide and silver oxide for a short time, and the hydrolysis product shown by paper chromatography in *n*-butanol–water to contain 5-*O*-methyl-D-ribose, a di-*O*-methyl-D-ribose fraction, and 2 : 3 : 5-tri-*O*-methyl-D-ribose. In *n*-butanol–boric acid the di-*O*-methyl-D-ribose fraction was resolved

into two components, one having the same R_P value in the two solvent systems and one travelling more slowly in presence of boric acid. The latter component was tentatively identified as 3 : 5-di-*O*-methyl-D-ribose since it was evidently capable of complex formation with boric acid. These two fractions were obtained pure by chromatographing the hydrolysate of the crude methylated product twice on thirty to forty large sheets of paper, and their designation as 2 : 5- and 3 : 5-di-*O*-methyl-D-ribose was confirmed by their conversions into 5-*O*-methyl-D-ribose phenylosazone and 3 : 5-di-*O*-methyl-D-ribose phenylosazone, respectively.

After this work was completed, 2-*O*-methyl-, 3-*O*-methyl-, 2 : 5-di-*O*-methyl-, and 3 : 5-di-*O*-methyl-D-ribose were reported as fission products of methylated uridylic acid *b* (Brown, Magrath, and Todd, *J.*, **1954**, 1422). The monomethyl sugars were obtained in amounts too small to allow of their full characterisation, but their behaviour on chromatography and on electrophoresis in presence of sodium borate was recorded. 3-*O*-Methyl-D-ribose was identified by the fact that it migrated electrophoretically at the same speed as 3 : 5-di-*O*-methyl-D-ribose, the assumption being that the two sugars form similar complexes with sodium borate. This would undoubtedly be true of complex-formation with boric acid. However, complex formation with sodium borate takes place more readily, and it is significant that while 2-*O*-methyl-D-ribose migrated electrophoretically in sodium borate, chromatography in presence of boric acid suggested that it does not form a complex under these conditions (Barker and Smith, *Chem. and Ind.*, 1954, 19). Complex-formation with boric acid is usually associated with a reduction of R_P value, but in a few cases, of which 3-*O*-methyl-D-ribose is one, the R_P value is increased. No explanation of this behaviour can be given, but it is believed that a different type of complex may be formed (cf. Bell and Northcote, *Chem. and Ind.*, 1954, 1328) with this sugar compared with others such as 3 : 5-di-*O*-methyl-D-ribose.

In the work of Brown, Magrath, and Todd (*loc. cit.*) 2 : 5- and 3 : 5-di-*O*-methyl-D-ribose were also separated by electrophoresis in presence of sodium borate but for purposes of identification, a mixture of the sugars was converted into a mixture of *p*-bromophenylosazones. We have found that removal of boric acid is less troublesome than the removal of sodium borate and we were able, by using partition chromatography, to isolate the components of a mixture for purposes of characterisation. Furthermore, removal of the last traces of boric acid is unnecessary before conversion into phenylosazones.

The work now described is in agreement with the identifications of methylated riboses described by Brown *et al.* (*loc. cit.*). The anomalous behaviour of 3-*O*-methyl-D-ribose, however, cannot yet be explained.

Experimental

M.p.s were determined on a Kofler block.

Paper Chromatography.—Two solvent systems were used : *n*-butanol saturated with water, and *n*-butanol saturated with both water and boric acid. Whatman No. 1 filter paper was used throughout, but for use with the *n*-butanol–boric acid systems the paper was first soaked in saturated aqueous boric acid and dried at room temperature.

2- *and* 3-O-*Methyl-*D*-ribose.*—Methyl 5-*O*-trityl-D-ribofuranoside (14 g.) was boiled with stirring for 10 min. with methyl iodide (50 c.c.) and silver oxide (8 g.). Silver oxide (8 g.) was added and heating continued for a further 10 min. After being cooled, silver salts were filtered off and washed with ether. The combined filtrate and washings were evaporated at 35° to a syrup (16·0 g.) which was hydrolysed and the product was resolved by paper chromatography (butanol–water) into fractions containing ribose, monomethylriboses, and 2 : 3-di-*O*-methylribose, and small quantities of the monomethylribose fraction were obtained by elution from the paper. The main part of the syrup was dissolved in benzene (300 c.c.) and run in three separate portions on neutral alumina (5 × 45 cm.). Elution with ether (1 l. each column) and evaporation of the solvent gave methyl 2 : 3-di-*O*-methyl-5-*O*-trityl-D-ribofuranoside (5 g.), which was rejected. Each column was then eluted with methanol (600 c.c. each), and evaporation gave a mixture of methyl 2- and methyl 3-*O*-methyl-5-*O*-trityl-D-ribofuranoside. The mixed product (10 g.) was heated on the steam-bath for 30 min. with 80% aqueous acetic acid

(100 c.c.) and cooled, and the triphenylmethanol filtered off. The filtrate was diluted with water (100 c.c.), filtered (charcoal), and extracted twice with chloroform (150 c.c.). The residual aqueous solution was evaporated under reduced pressure to a syrup from which ethanol (200 c.c.) was distilled three times to remove the last trace of acetic acid. The residual syrup was boiled for 1 hr. with 0·04N-hydrochloric acid, cooled, freed from chloride ions by being ground with silver oxide and filtered (charcoal), and evaporated under reduced pressure to a syrup (3 g.). Approximately one-third of this material was chromatographed on thirty large sheets of paper (butanol–boric acid system), and crude 2-*O*-methyl-D-ribose (Component *A*) (R_F, 0·3; 0·29 g.) and 3-*O*-methyl-D-ribose (Component *B*) (R_F, 0·55; 0·29 g.) were eluted with methanol from appropriate areas of the papers. After removal of the solvent under reduced pressure boric acid was removed by repeated distillation with methanol. The resulting sugars were separately converted into the methyl furanosides which were purified by sublimation at 0·01 mm. These were separately hydrolysed with 0·04N-hydrochloric acid as described above and yielded, respectively, 2-*O*-*methyl*-D-*ribose*, $[\alpha]_D^{20}$ −32° (*c*, 1·09 in MeOH) (Found: OMe, 18·9. $C_6H_{12}O_5$ requires OMe, 19·0%), and 3-*O*-*methyl*-D-*ribose*, $[\alpha]_D^{20}$ +7·5 (*c*, 0·6 in MeOH) (Found: OMe, 18·0%).

D-*Ribose Phenylosazone from* 2-O-*Methyl*-D-*ribose*.—2-*O*-Methyl-D-ribose (0·02 g.), 2N-acetic acid (3·5 c.c.), and phenylhydrazine (0·2 c.c.) were heated at 100° for 4·5 hr. After cooling, the solid was collected, dissolved in benzene (10 c.c.) and run on to neutral alumina. D-Ribose phenylosazone was obtained by elution with benzene–ether (1 : 1) and removal of the solvent. It had m. p. 160° (Found: N, 16·7. Calc. for $C_{17}H_{20}O_3N_4$: N, 17%).

3-O-*Methyl*-D-*ribose Phenylosazone*.—3-*O*-Methyl-D-ribose (0·035 g.), 2N-acetic acid (3·5 c.c.), and phenylhydrazine (0·2 c.c.) were heated at 100° for 2 hr. and the solid obtained as described above was eluted from neutral alumina with benzene containing 30% of ether. The product had m. p. 135°, not depressed by the osazone prepared from 2 : 3-di-*O*-methyl-D-ribose (Found: OMe, 7·7. Calc. for $C_{18}H_{22}O_3N_4$: OMe, 9·0%).

Methylation of Methyl iso*Propylidene*-D-*ribopyranoside*.—The crude condensation product of methyl D-ribopyranoside and acetone (Levene and Stiller, *loc. cit.*) was fractionally distilled and had b. p. 170—175° (bath temp.)/0·01 mm., n_D^{16} 1·4596 (Found: C, 51·1; H, 8·1; OMe, 14·6. Calc. for $C_9H_{16}O_5$: C, 52·4; H, 7·9; OMe, 15·2%). This material (0·64 g.) was stirred and boiled with methyl iodide (10 c.c.), and silver oxide (1 g.) was added every hour during 6 hr. The filtrate from silver salts was evaporated leaving a syrupy product having b. p. 70—80° (bath temp.)/0·02 mm., n_D^{17} 1·4478 (Found: C, 55·0; H, 8·2; OMe, 26·2. Calc. for $C_{10}H_{18}O_5$: C, 55·0; H, 8·3; OMe, 28·5%).

Chromatography of 2-, 4-, *and* 5-O-*Methyl*-D-*ribose*.—The mixed methylated products obtained from methyl *iso*propylidene-D-ribopyranoside were hydrolysed with 0·04-hydrochloric acid as described above and, after removal of chloride ions, were dissolved in 0·01M-sodium tetraborate (5 c.c.) and run on to Dowex-1 (1 × 10 cm.) in the borate form. The column was eluted with 0·01M-sodium tetraborate, and samples (10 c.c.) were analysed for pentose by a modification of Brown's orcinol method (*Arch. Biochem.*, 1946, **11**, 270). Combined solutions of fraction 1 and fraction 2 were separately freed from sodium ions as described by Khym and Zill (*J. Amer. Chem. Soc.*, 1951, **73**, 2399), and aliquot parts were chromatographed on paper (*n*-butanol–boric acid). Fraction 1 showed spots with R_F values 0·19 and 0·27. Fraction 2 showed a single spot having R_F 0·30.

Preparation and Methylation of Benzylidene Derivatives.—(a) *From methyl* D-*ribofuranoside*. Methyl D-ribofuranoside (6·8 g.), benzaldehyde (35 g.), and powdered anhydrous zinc chloride (8 g.) were shaken in a closed flask for 24 hr. The viscous mass was triturated with light petroleum to remove some benzaldehyde, taken up in chloroform and washed successively with water and aqueous sodium hydrogen carbonate, and then concentrated to a syrup which was heated at 60°/0·05 mm. The residue was steam-distilled *in vacuo* to remove the last trace of benzaldehyde and extracted with chloroform; the extract was washed with aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated under reduced pressure to yield syrupy *methyl* 2 : 3-*O*-*benzylidene*-D-*ribofuranoside* (8·9 g.), b. p. 100° (bath temp.)/10^{-4} mm., n_D^{20} 1·5225, $[\alpha]_D^{20}$ −41·0° (*c*, 8·49 in $CHCl_3$) (Found: C, 61·3; H, 6·5; OMe, 11·7. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·35; OMe, 12·3%). During a few days, the compound undergoes slight decomposition resulting in the reappearance of the smell of benzaldehyde. This may be related to the phenomenon observed in the case of methyl 3 : 4-*O*-benzylidene-β-L-arabinoside (Oldham and Honeyman, *J.*, 1946, 986).

The methyl 2 : 3-*O*-benzylidene-D-ribofuranoside was methylated with methyl iodide and silver oxide in the usual way. After filtration from silver salts and removal of methyl iodide,

the residue (4 g.) was dissolved in ether and run on to alumina (Peter Spence, Grade H). Elution with ether gave, after removal of solvent, syrupy *methyl* 2 : 3-O-*benzylidene*-5-O-*methyl*-D-*ribofuranoside* (1·4 g.) which was sublimed at 100°/10^{-3} mm. It had $[\alpha]_D^{20}$ −55·6° (*c*, 4·1 in $CHCl_3$), n_D^{17} 1·5161 (Found : C, 62·9; H, 6·6; OMe, 22·4. $C_{14}H_{18}O_5$ requires C, 63·0; H, 6·8; OMe, 23·3%). A small sample, after hydrolysis with 0·04N-hydrochloric acid as described above, showed a single spot on paper chromatography, having R_F 0·39 and 0·19 in *n*-butanol–water and *n*-butanol–boric acid, respectively.

(b) *From methyl* D-*ribopyranoside*. Methyl β-D-ribopyranoside (Minsaas, *Annalen*, **1934**, **512**, 286; Barker and Smith, *J.*, **1954**, 2151) (1·03 g.) was condensed with benzaldehyde (45 g.) as described above. Sublimation of the syrupy product gave methyl 2 : 3-*O*-benzylidene-D-ribofuranoside (Found : C, 62·7; H, 6·9; OMe, 12·7%), which was methylated with methyl iodide and silver oxide. After hydrolysis of the syrupy product, a single spot was obtained on paper chromatography, having R_F 0·39 and 0·19 in *n*-butanol–water and *n*-butanol–boric acid, respectively.

(c) *From guanosine*. 2′ : 3′-*O*-Benzylideneguanosine (Bredereck and Berger, *Ber.*, **1940**, **73**, 1124) (2·8 g.) was methylated by the method described for purine nucleosides (Anderson, Barker, Gulland, and Lock, *J.*, **1952**, 369). Hydrolysis of the crude product was effected as described above and the hydrolysate was chromatographed on paper. In *n*-butanol–water, a spot (R_F 0·39) corresponding to 5-*O*-methyl-D-ribose was observed besides a faint spot (R_F 0·17) corresponding to D-ribose. In *n*-butanol–boric acid, a single spot (R_F 0·19) was observed, since the above two sugars have identical R_F values in this solvent system.

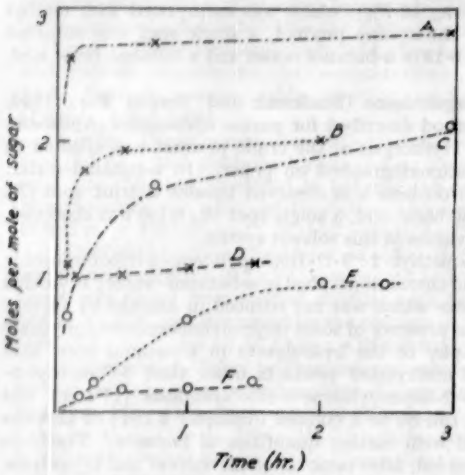
5-O-*Methyl*-D-*ribose*.—Crude methyl 5-*O*-methyl-2 : 3-*O*-*iso*propylidene-D-ribofuranoside (Levene and Stiller, *loc. cit.*) was hydrolysed and chromatographed in *n*-butanol–water; it yielded an appreciable quantity of unmethylated ribose which was not reduced in amount by further methylation. This is believed to be due to the presence of some *iso*propylideneribose anhydride (Levene and Stiller, *loc. cit.*). Chromatography of the hydrolysate in *n*-butanol–boric acid indicated the presence of small amounts of methylated products other than 5-*O*-methyl-D-ribose. The crude methyl 5-*O*-methyl-2 : 3-*O*-*iso*propylidene-D-ribofuranoside (11·4 g.) was therefore dissolved in benzene (100 c.c.) and run on to a column (diameter 5 cm.) of alumina (Peter Spence, grade H) (400 g.) and eluted with further quantities of benzene. Fractions (50 c.c.) were collected and samples were examined, after removal of the solvent and hydrolysis, by paper chromatography in *n*-butanol–water and in *n*-butanol–boric acid. Those fractions which yielded only 5-*O*-methyl-D-ribose were pooled, hydrolysed by boiling 0·1N-sulphuric acid (150 c.c.) for 1 hr., and after removal of sulphate ions with Amberlite IR-4B (carbonate), were concentrated under reduced pressure to yield syrupy 5-*O*-methyl-D-ribose (3·0 g.) (Found : C, 43·6; H, 7·1; OMe, 18·8. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·3; OMe, 18·9%). It yielded a phenylosazone, m. p. 150° (Found : C, 63·2; H, 6·2; N, 15·6; OMe, 9·1. Calc. for $C_{18}H_{22}O_3N_4$: C, 63·1; H, 6·5; N, 16·4; OMe, 9·1%).

5-O-*Methyl*-D-*ribonolactone*.—5-*O*-Methyl-D-ribose (0·5 g.), water (10 c.c.), and bromine (1 c.c.) were kept in a stoppered flask for 4 days at room temperature. Excess of bromine was removed by aeration, bromide ions by grinding with silver oxide and filtration, and silver ions with hydrogen sulphide. The filtrate from silver sulphide was evaporated under reduced pressure to yield a syrupy *lactone* which crystallised (0·42 g.), and after recrystallisation from ethyl acetate had m. p. 109—110°, $[\alpha]_D^{18}$ +27·4° (initial value), +26·4° (36 min.), +25·2° (84 min.), +21·9° (180 min.), +20·0° (238 min.), +17·2° (324 min.), +15·3° (420 min.) (*c*, 8·5 in H_2O) (Found : C, 44·3; H, 6·3. $C_6H_{10}O_5$ requires C, 44·4; H, 6·2%).

2 : 5-*Di*-O-*methyl*-D-*ribose and* 3 : 5-*Di*-O-*methyl*-D-*ribose*.—A solution of chromatographically homogeneous 5-*O*-methyl-D-ribose (2·9 g.) in methanol (200 c.c.) containing 1% of hydrogen chloride was set aside at room temperature for 1·5 hr. After removal of chloride ions by grinding with silver carbonate and filtration, methanol was removed under reduced pressure. The remaining syrupy methyl 5-*O*-methyl-D-ribofuranoside was partially methylated as described for methyl 5-*O*-trityl-D-ribofuranoside and the product (3·1 g.) was boiled for 1·25 hr. with 0·1N-sulphuric acid (100 c.c.). Sulphate ions were removed by means of Amberlite IR-4B (carbonate), and the neutral solution was concentrated under reduced pressure to a syrup which was chromatographed (*n*-butanol–boric acid system) on 40 large sheets of paper. Appropriate areas of the paper were eluted with water and after removal of solvent and of boric acid by repeated distillation with methanol, the crude 2 : 5- and 3 : 5-di-*O*-methyl-D-ribose fractions were separately re-chromatographed in the same way on 30 sheets each. The two fractions were eluted from the chromatograms and freed from solvent and boric acid as before to give, respectively, syrupy 2 : 5-*di*-O-*methyl*-D-*ribose* (0·5 g.) (Found : C, 47·6; H, 7·8; OMe, 32·6. $C_7H_{14}O_5$ requires C,

47·2; H, 7·9; OMe, 34·8%) and **3 : 5-*di*-O-*methyl*-D-*ribose*** (0·4 g.) (Found : C, 46·5; H, 7·6; OMe, 32·7%).

3 : 5-*Di*-O-*methyl*-D-*ribose Phenylosazone*.—3 : 5-Di-*O*-methyl-D-ribose (0·09 g.) was heated on the steam-bath for 10 min. with phenylhydrazine (0·2 c.c.) and 2N-acetic acid (5 c.c.). The solid was collected, dissolved in benzene (10 c.c.), and run on to neutral alumina (40 × 2 cm.). The column was washed with benzene (100 c.c.), and the osazone was then eluted with benzene–ether (1 : 1) (100 c.c.). After removal of the solvent, the osazone (0·05 g.) was crystallised from methanol. It had m. p. 161° (Found : C, 63·8; H, 7·2; N, 15·6; OMe, 16·3. Calc. for $C_{19}H_{24}O_3N_4$: C, 64·0; H, 6·7; N, 15·7; OMe, 17·4%).



D-Ribose derivative	HIO_4 consumed	Acid produced
2-*O*-Methyl	*B*	*E*
3-*O*-Methyl	*D*	*F*
5-*O*-Methyl	*A*	*C*

***Preparation of the Osazone from* 2 : 5-*Di*-O-*methyl*-D-*ribose*.**—The osazone was prepared by the method described above except that heating was continued for 6 hr. and 500 c.c. of benzene were used for the elution of the osazone from the alumina. The 5-*O*-methyl-D-ribose phenylosazone crystallised from methanol and had m. p. 150°, not depressed by the osazone prepared from 5-*O*-methyl-D-ribose (Found : C, 62·9; H, 6·1; N, 15·6; OMe, 8·8. Calc. for $C_{18}H_{22}O_3N_4$: C, 63·1; H, 6·5; N, 16·4; OMe, 9·1%).

***Periodate Oxidations*.**—2-, 3-, and 5-*O*-Methyl-D-ribose were oxidised by sodium metaperiodate and the reactions were followed as previously described (Barker and Smith, preceding paper). The rates of consumption of periodate and the released acid are shown in the Figure.

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The Chemistry of Extractives from Hardwoods. Part XXIII. The Isolation of a New Triterpene (Terminolic Acid) from* Terminalia ivorensis.

By F. E. King, T. J. King, and J. M. Ross.

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By the successive extraction of idigbo, a hardwood derived from *Terminalia ivorensis*, with light petroleum, ether, and ethanol, " β "-sitosterol, a new triterpene (terminolic acid), $C_{30}H_{48}O_6$, and ellagic acid have been isolated. Terminolic acid, a pentacyclic tertiary monocarboxylic acid containing one double bond and four hydroxyl groups, of which two are adjacent, is a member of the β-amyrin–oleanolic acid series.

The West African tree *Terminalia ivorensis* yields a commercial timber known as idigbo or black afara. The colour of the heartwood varies from pale yellow to red-brown and the alternative name, which refers to the appearance of the bark, is intended to distinguish it from white afara or limba, the wood of a related species, *Terminalia superba*. Idigbo is resistant to wood-rotting fungi and finds many constructional uses but has the undesirable property of developing yellow stains in contact with dilute alkalis including soap solutions. The description which follows gives details of the first chemical investigation of the extraneous constituents of the wood.

Boiling light petroleum removed a small quantity (0·3%) of a viscous oil. This slowly deposited a crystalline solid which was identified as " β "-sitosterol. Further extraction with boiling ether produced an amorphous powder which separated from the hot solvent and was obtained crystalline after some preliminary purification, by repeated dissolution in acetone or more conveniently through the sparingly soluble sodium salt. The product, a new triterpene $C_{30}H_{48}O_6$, hereafter called terminolic acid, in some cases constituted approximately 1·5% of the wood.

A large amount of amorphous solid was extracted by ethanol, and crystallisation of the portion insoluble in acetic acid yielded ellagic acid. It is to this constituent that the yellow staining of the wood by alkalis is due. Ellagic acid has been found in other *Terminalia* species, *e.g.*, the fruit of *T. chebula* (Perkin and Nierenstein, *J.*, 1905, **87**, 1412) and the wood of *T. arjuna* (King, King, and Ross, *J.*, 1954, 3995).

Terminolic acid is only weakly acidic, being virtually insoluble in sodium hydrogen carbonate solution, and with aqueous sodium hydroxide above 0·5N its solubility is inhibited by the formation of the sodium salt. Treatment with diazomethane or with sodium hydroxide–methyl sulphate gave the ester, methyl terminolate, $C_{31}H_{50}O_6$. The hindered character of the carboxyl group was evident from its inertness to Fischer–Speier conditions of esterification, and from the inability of its esters to be hydrolysed under normal conditions. The acid resisted reduction by catalytic and chemical methods, and gave only a very weak yellow colour with tetranitromethane, but the coloration was more pronounced with the ester and acetate. The presence of a double bond was proved by quantitative oxidation with monoperphthalic acid, analysis of the product agreeing with the addition of one atom of oxygen. From this evidence in conjunction with the molecular formula it may be concluded that terminolic acid is pentacyclic. The infra-red absorption of methyl terminolate (bands at 800 to 850 cm.$^{-1}$ and weak shoulder at 1640—1670 cm.$^{-1}$) was indicative of a trisubstituted olefinic bond (cf. Jeger, Ruzicka, *et al.*, *Helv. Chim. Acta*, 1950, **33**, 672, 687, 711, 1050; Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402). Its situation with respect to the carboxyl group was evident from the formation with bromine in acetic acid of a highly crystalline bromo-lactone, thus denoting a βγ- or γδ-unsaturated acid, analogy with other triterpene acids and the infra-red observations just mentioned favouring the latter possibility. The susceptibility of the compound to per-acid oxidation and the easy formation of the bromo-lactone place terminolic acid in the β-amyrin–oleanolic acid group of pentacyclic triterpenes.

* Part XXII, *J.*, 1955, 1117.

Analyses of the acid and methyl ester acetates, which were obtained crystalline only after considerable manipulation, proved the remaining four oxygen atoms to be present as hydroxyl groups.

Methyl terminolate tetra-acetate is oxidised by selenium dioxide to a substance which though non-crystalline is substantially the 11 : 13(18)-dehydro-derivative since its ultra-violet absorption closely resembles that of similar triterpenes, *e.g.*, dehydro-oleanolic acid (Barton and Holness, *J.*, 1952, 78). More vigorous oxidation with this reagent gave the 10 : 13-diene-12 : 19-dione, similarly identified by its light absorption, thus affording further support for the relation of terminolic acid to the β-amyrin series.

The reaction of terminolic bromo-lactone with methanolic potassium hydroxide led to the β-epoxide (see King, King, and Ross, *loc. cit.*). However, this suffered partial rearrangement when crystallised and so could not be obtained pure; it was converted by the action of hydrogen chloride in chloroform into the methyl dihydro-12-oxo-ester. The monoperphthalic acid oxidation product of methyl terminolate on the other hand, as with that of methyl oleanolate acetate (Picard and Spring, *J.*, 1940, 1389), consists of the stable α-epoxide. A comparison of the infra-red spectra of the α-epoxide and the saturated ketone confirms their respective structures, the epoxide exhibiting a single carbonyl peak at 1712 cm.$^{-1}$, due to the ester grouping, whereas the dihydro-oxo-ester has a broad peak at 1685 cm.$^{-1}$, with a shoulder at 1715 cm.$^{-1}$ (determinations with suspensions in Nujol owing to the insolubility of the compounds in carbon tetrachloride). The authors thank Dr. G. D. Meakins, University of Manchester, for these measurements which were undertaken through the kindness of Professor E. R. H. Jones, F.R.S. When the epoxide is treated with hot acetic and hydrochloric acids it yields the methyl dihydro-oxo-ester tetra-acetate identical with that obtained from acetylation of the saturated ketone and by the action of hot acetic acid–hydrogen peroxide on methyl terminolate tetra-acetate. Hydrolysis of the actate yields methyl dihydro-12-oxoterminolate. The marked negative shift in specific rotation when passing from methyl terminolate (+40°) to the dihydro-12-oxo-ester (−45°) is similar to that for the change of methyl arjunolate (+68°) to methyl dihydro-12-oxoarjunolate (−30).*

Attempts to oxidise terminolic acid to keto-compounds, and thence by reduction to relate them to known triterpenes, failed to yield any crystalline oxidation products. With sodium periodate an amorphous product was obtained which gave a precipitate with 2 : 4-dinitrophenylhydrazine solution, thus disclosing the presence of a 1 : 2-glycol unit; a quantitative determination in which it was ascertained that only one molecule of the oxidising agent was required proved the glycol unit to be isolated from the remaining hydroxyl groups.

As with the corresponding derivative of arjunolic acid (Part XVIII), reductive fission of the product obtained in the lead tetra-acetate oxidation of terminolic bromo-lactone took place without the evolution of carbon dioxide. Hence it is apparent that the α-glycol cannot be adjacent to the carboxyl group where it would give rise on oxidation to a β-carbonylic acid. Its location is, in fact, by this observation restricted to ring A or B. Further experiments, to be reported shortly, confirm the expectation based on the botanical relationship of the respective species that the new triterpene is a hydroxyarjunolic acid.

Experimental

Specimens for analysis, except where otherwise indicated, were dried at 120°/0·1 mm. for 2 hr. Alcoholic solutions were used for measurements of ultra-violet absorption spectra and chloroform for the optical rotations (determined at room temperature).

Extraction of Terminalia ivorensis *Heartwood.*—The botanical origin of commercial idigbo used in the research was kindly verified by Mr. B. J. Rendle, D.S.I.R. Forest Products Research Laboratory. Continuous extraction of the coarsely powdered wood (3·5 kg.) with boiling light petroleum (b. p. 60—80°) for 18 hr. afforded a red-brown viscous oil (10—12 g., 0·3%). Crystalline solid which gradually separated was removed from the oil with boiling methanol. By repeated crystallisation from methanol "β"-sitosterol (1 g.) was obtained as plates, m. p. 136—137°, $[\alpha]_D$ −34° (*c*, 2·03), and its acetate had m. p. 124—125°, $[\alpha]_D$ −38° (*c*, 1·13) (Found: C,

* The specific rotation of methyl dihydro-12-oxoarjunolate was misprinted as +30° in *J.*, 1954, 4000.

81·3; H, 11·5. Calc. for $C_{31}H_{52}O_2$: C, 81·6; H, 11·4%). Other derivatives were the benzoate, m. p. and mixed m. p. 145—146° (Found: C, 82·8; H, 10·4. Calc. for $C_{36}H_{54}O_2$: C, 83·3; H, 10·5%) and *p*-nitrobenzoate, m. p. 181—182° (Found: C, 76·5; H, 9·0. Calc. for $C_{36}H_{53}O_4N$: C, 76·7; H, 9·5%), which likewise closely resembled published descriptions, summarised, for example, in *J.*, 1953, 1193.

The wood was next treated with boiling ether, 18 hours sufficing for complete removal of the extractable triterpene, part of which separated as a free-flowing amorphous cream powder (maximum yield 50—55 g., 1·5%). The amount of this extractive varied from specimen to specimen of the wood and in some was almost nil.

Finally, the wood was exhaustively extracted with boiling ethanol and the solution concentrated to 1 l. The solid which was then deposited was crystallised from pyridine and yielded ellagic acid (19·5 g.). After further crystallisation from pyridine (charcoal) it separated in pale yellow needles, m. p. >360° (Found: C, 55·4; H, 2·2. Calc. for $C_{14}H_6O_8$: C, 55·6; H, 2·0%): max. at 255 (log ε, 4·69) and 365 mμ (log ε, 4·07). The tetra-acetate, cream coloured leaflets from acetic anhydride, had m. p. 340—343° (Perkin and Nierenstein, *loc. cit.*, give 343—346°). The tetramethyl ether, plates, m. p. 343—344°, from acetic anhydride, was prepared with diazomethane in methanol–ether (Goldschmidt, *Monatsh.*, 1905, **26**, 1139) (Found: C, 59·8; H, 3·7. Calc. for $C_{18}H_{14}O_8$: C, 60·3; H, 3·9%), unchanged ellagic acid being removed with a little boiling pyridine. Complete evaporation of the alcohol gave a brown powder (5·47 g.) from which a further quantity of ellagic acid (4·2 g./50 g.) was isolated by treatment with dioxan (2 c.c./g.).

Terminolic Acid.—(*a*) The amorphous product obtained by ether-extraction was digested with acetic acid (2 c.c./g.) at 70° and the solution filtered from the residue of ellagic acid. The addition of water to the filtrate precipitated the dissolved solid which was dried and extracted in batches (20 g.) (Soxhlet) with acetone (125 c.c.). With the appearance of solid from the solution the solvent was changed, the process being repeated until only weakly coloured solutions were obtained. Concentration of these solutions gave crystalline *terminolic acid* (7 g.) which separated from acetone in minute prisms, m. p. 335—336°. The repeatedly crystallised analytical specimen had m. p. 347°, $[\alpha]_D$ +42° (*c*, 0·11 in EtOH) (Found: C, 71·2, 71·2, 71·6; H, 9·3, 9·4, 9·6; active H, 0·76%; equiv. 510, 498. $C_{30}H_{48}O_6$ requires C, 71·4; H, 9·5; 5 active H, 0·99%; equiv., 504).

(*b*) Later extractions were performed without previous treatment with light petroleum; for example, the whole product extracted from 7 kg. of wood was dissolved in boiling methanol (700 c.c.), and the solution filtered and made weakly alkaline with concentrated aqueous sodium hydroxide. When the sodium ellagate which separated in the cold had been removed, the solution was diluted with water to 1500 c.c. and treated with excess of sodium hydroxide. By concentrating the solution on a steam-bath until a test portion crystallised on cooling, terminolic acid was isolated as the sodium salt, obtained as colourless silky needles by recrystallisation from the aqueous methanolic alkali, fairly soluble in alcohol but only sparingly in dilute aqueous sodium hydroxide (yields 20—60 g.).

With cold concentrated sulphuric acid the triterpene exhibits a yellow colour slowly changing to violet; in the Liebermann–Burchard test it reacts pink, changing to red-brown, and the colour sequence with Tschugaieff's acetyl chloride–zinc chloride reagent is orange—deep-red—brown. Terminolic acid is freely soluble in both hot and cold acetic acid, dioxan, pyridine and 2-ethoxyethanol; it dissolves sparingly in acetone and the simple alcohols.

Methyl Terminolate.—Diazomethane in ether was added to a suspension of the purified acid in methanol and after 2 hr. the solvents were evaporated. The residue was recrystallised from methanol, to give *methyl terminolate* (80—90%), m. p. 160—170°, also obtained in high yield by shaking the acid or the sodium salt with methyl sulphate and excess of 1% methanolic sodium hydroxide. The ester crystallised in prisms, m. p. (slow heating) 165—168°, $[\alpha]_D$ +40° (*c*, 0·78) (Found, after drying at 150° *in vacuo*: C, 71·8; H, 9·6; OMe, 7·2. $C_{31}H_{50}O_6$ requires C, 71·8; H, 9·65; OMe, 6·0%). The ester was unattacked when heated under reflux with 10% alcoholic potassium hydroxide for 4 hr. *Ethyl terminolate*, prepared with ethyl sulphate and 1% alcoholic sodium hydroxide, crystallised from ethanol in plates, m. p. 164—165°, $[\alpha]_D$ +41° (*c*, 1·06) (Found, after drying at 150° *in vacuo*: C, 72·2; H, 10·1; OEt, 8·5. $C_{33}H_{52}O_6$ requires C, 72·2; H, 9·8; OEt, 8·5%).

p-*Nitrobenzyl terminolate*, obtained by refluxing the acid with 0·5% alcoholic sodium hydroxide and *p*-nitrobenzyl bromide for 1 hr., crystallised from ethanol in prisms, m. p. 242° (Found: C, 69·4; H, 8·0; N, 2·3. $C_{37}H_{53}O_8N$ requires C, 69·5; H, 8·3; N, 2·2%).

To an ethanol solution (25 c.c.) of methyl terminolate (0·1 g.) aqueous sodium metaperiodate

(2 c.c.; 0·363M) was added. Titration of an aliquot in the usual way after 3 hr. indicated the oxidation of one α-glycol unit (Found: 0·97 and 1·09). No further appreciable oxidation had occurred after 24 hr.

Terminolic Acid Tetra-acetate.—The usual procedures, including chromatography of light petroleum–benzene solutions on alumina, failed to effect crystallisation of the amorphous products obtained with the common acetylating agents. That formed from acetic anhydride–perchloric acid was distilled at 260—290°/10^{-5} mm. and dissolved in hot *cyclo*hexane, and after collection from the cold solution appeared to be the *tetra-acetate* (Found: C, 67·8; H, 8·4; OAc, 22·8. $C_{38}H_{56}O_{10}$ requires C, 67·9; H, 8·3; 4OAc, 25·6%). Chromatography by absorption on acid-washed alumina in light petroleum–benzene (4 : 1) and elution with benzene eventually gave the crystalline actate in low yield as leaflets, m. p. 217° (from methanol), $[\alpha]_D$ −12·5° (*c*, 0·36) (Found: C, 67·9; H, 8·3%). The sparing solubility of both acetate and its saponification product in the alcoholic alkaline reagent may account for the low OAc value.

Methyl Terminolate Tetra-acetate.—Acetylation (acetic anhydride–pyridine at room temperature overnight) of pure methyl terminolate yielded an amorphous product which could be obtained crystalline by absorption on acid-washed alumina from benzene solution followed by elution with the same solvent. The *ester tetra-acetate* separated from methanol in leaflets, m. p. after drying *ca.* 187—189° (Found: C, 68·0; H, 8·15; OMe, 5·6; OAc, 22·9. $C_{39}H_{58}O_{10}$ requires C, 68·2; H, 8·4; OMe, 4·5; 4OAc, 25%).

Oxidation of Methyl Terminolate Tetra-acetate with Selenium Dioxide.—(*a*) A solution of methyl terminolate tetra-acetate (0·97 g.) in acetic acid (50 c.c.) containing sublimed selenium dioxide (0·45 g.) was heated under reflux for 15 hr. After filtration from selenium, the solution was evaporated under diminished pressure, and the residue dissolved in ether which was then washed with aqueous sodium hydrogen carbonate and water and evaporated. The amber gummy residue (0·96 g.), dissolved in benzene and filtered through alumina, gave 0·88 g. of non-crystalline eluate. This was dissolved in benzene (2 c.c.), and the solution diluted to 25 c.c. with light petroleum (b. p. 60—80°). Chromatography on alumina (Grade H, 25 g.) gave the following fractions: 1, eluant 1220 c.c. of 1 : 3 light petroleum–benzene, 235 mg.; 2, eluant 600 c.c., of ether, 160 mg.; 3, eluant 800 c.c., of methanol, 110 mg. The fractions separated from acetone as amorphous solids with the following light absorption: 1, max. 243, 250·5, 260 mμ (log ε, 4·37, 4·42, 4·23); 3, max. 242, 250·5, 259·5 mμ (log ε, 4·23, 4·40, 4·15). Dehydro-oleanolic acid (Barton and Holness, *J.*, 1952, 78) has max. 242, 252, 261 mμ (log ε, 4·41, 4·46, 4·28).

(*b*) The ester acetate (0·5 g.) and excess (0·5 g.) of selenium dioxide were heated in boiling acetic acid for 24 hr. The product, freed from selenium and acetic acid, was dissolved in benzene, and the solution washed with aqueous sodium hydrogen carbonate. Chromatography on alumina and elution with benzene removed the 11 : 13(18)-diene, and further elution with ether yielded an uncrystallisable product (100 mg.) which however possessed the light absorption of a 10 : 13-diene-12 : 19-dione, *viz.*, $\lambda_{max.}$ 276 mμ (ε 11,300). Ruzicka, Jeger, and Winter (*Helv. Chim. Acta*, 1943, **26**, 265) found $\lambda_{max.}$ 275 mμ (ε 12,500) for the diene-dione from methyl oleanolate acetate.

Terminolic Bromo-lactone.—To a stirred solution of terminolic acid (2 g.) and sodium acetate (8 g.) in acetic acid (90 c.c.), 3% bromine–acetic acid (50 c.c.) was added during ½ hr. After a further ½ hr. the mixture was poured into water containing sodium thiosulphate (4 g.), and the precipitate collected, washed with aqueous sodium hydrogen carbonate and water, and dried. The *bromo-lactone* crystallised from methanol in leaflets (1·6 g.), m. p. 232° (decomp.), $[\alpha]_D$ +32° (*c*, 0·87) (Found: C, 61·7; H, 8·0; Br, 12·5. $C_{30}H_{47}O_6Br$ requires C, 61·7; H, 8·1; Br, 13·6%).

Methyl Dihydro-12-oxoterminolate.—The bromo-lactone (2·3 g.) was refluxed with 3% methanolic potassium hydroxide (50 c.c.) for 1 hr. and diluted with water until crystallisation began. The resulting β-epoxide (1·4 g.) crystallised from aqueous methanol in needles, m. p. *ca.* 250° which became indefinite on further crystallisation. A solution of the epoxide in chloroform (25 c.c.), treated with a stream of hydrogen chloride, gave *methyl dihydro-12-oxoterminolate* which was isolated by evaporation of the solvent. Crystallised from methanol it formed rectangular tablets (1·1 g.) exhibiting a dual m. p., *ca.* 200—205° and 317—321°, $[\alpha]_D$ −45° (*c*, 0·93) (Found, in a specimen dried at 150°/0·1 mm.: C, 70·0; H, 9·5. $C_{31}H_{50}O_7$ requires C, 69·6; H, 9·4%).

Acetylation of the dihydro-oxo-ester (0·5 g.) by refluxing acetic anhydride (3 c.c.) and pyridine (1 c.c.) for 1·5 hr. yielded *methyl dihydro-12-oxoterminolate tetra-acetate* which readily crystallised from methanol in long, fine needles, m. p. 284—285°, $[\alpha]_D$ −39° (*c*, 0·44) (Found:

C, 66·9; H, 8·2. $C_{39}H_{58}O_{11}$ requires C, 66·7; H, 8·3%); light absorption, $\lambda_{max.}$ 286 mμ (ε 40). The acetate was also obtained (yield 70%) by oxidation of methyl terminolate tetra-acetate with hot acetic acid–hydrogen peroxide for 2 hr.

Methyl 12 : 13-*Epoxyterminolate*.—A solution of methyl terminolate (0·985 g.) in ether (20 c.c.) was mixed with ethereal monoperphthalic acid (5 c.c.; 0·5N), and the mixture maintained at 0—2°. Portions removed after 1, 2, 6, and 18 days showed a consumption of 0·58, 0·66, 0·97, and 1·03 mols. respectively of the per-acid.

A solution similarly obtained from 1·0 g. of the methyl ester was shaken with aqueous sodium hydrogen carbonate; removal of the solvent gave the *epoxide* which crystallised from methanol in elongated prisms, m. p. 175°, $[\alpha]_D$ +7·7° (*c*, 0·92) (Found, in a specimen dried at 150°/0·1 mm.: C, 69·7; H, 9·4; OMe, 6·6. $C_{31}H_{50}O_7$ requires C, 69·6; H, 9·4; OMe, 5·8%).

Isomerisation of the 12 : 13-*Epoxide to Methyl Dihydro*-12-*oxoterminolate Tetra-acetate*.—A solution of the epoxide (0·5 g.) in acetic acid (18 c.c.) was treated with 10% hydrochloric acid (0·5 c.c.), heated on a steam-bath for 8 hr., poured into water, and worked up in the usual way; the ester tetra-acetate crystallised from methanol (Norite) in silky needles, m. p. and mixed m. p. 281—283° (Found: C, 66·8; H, 8·8%).

Hydrolysis by refluxing 5% methanolic potash for 1·5 hr. gave the methyl dihydro-12-oxoterminolate in rectangular plates, m. p. 195° and 312—317°.

Methyl 12 : 13-*Epoxyterminolate Tetra-acetate*.—Methyl terminolate tetra-acetate (1·1 g.) in ether (20 c.c.) was treated with ethereal monoperphthalic acid (50 c.c.; 0·3N) and kept at 0—2° for 12 days. On working up in the usual way the acetylated *epoxy-ester* was obtained as a colourless solid (1·1 g.) which could not be crystallised (Found: C, 66·3; H, 8·0. $C_{39}H_{58}O_{11}$ requires C, 66·7; H, 8·3%).

Reduction of Terminolic Bromo-lactone.—(a) *With zinc powder in acetic acid*. The bromo-lactone (0·8 g.) in acetic acid was heated with zinc powder (5 g.) on a steam-bath for 2 hr. The liquid was then filtered and the product precipitated with water; crystallised from methanol it gave terminolic acid (0·56 g.), which after repeated crystallisation from methanol, and finally butanol, formed large prisms, m. p. 342—344° (Found: C, 71·8; H, 9·4%).

(b) *With sodium amalgam*. To an ethanolic solution (40 c.c.) of terminolic bromo-lactone (0·82 g.) were added 3% sodium amalgam (5 g.) and a few drops acetic acid. The mixture was refluxed on a steam-bath for 2 hr. and then worked up by pouring the solution into water and acidifying it. The acid, crystallised from methanol, had m. p. 338—339° (slight decomp.).

Oxidation of Terminolic Bromo-lactone with Lead Tetra-acetate.—A warm solution of lead tetra-acetate (*ca.* 6 g.) in acetic acid (125 c.c.) was added to the bromo-lactone (4·84 g.) in acetic acid (125 c.c.) (temperature of mixture, 32°). After 12·5 hr. at 20° the excess of reagent was destroyed with ethylene glycol, and the mixture poured into water. The dried precipitate separated from methanol in a semigelatinous state but the product (3·4 g.) eventually crystallised from methanol and on further crystallisation gave colourless needles, m. p. 216—217° (decomp.) (Found, in a specimen dried at 150°/0·1 mm.: C, 61·8; H, 7·8. $C_{30}H_{45}O_6Br$ requires C, 61·9; H, 7·7%).

A solution of the oxidation product (0·91 g.) in acetic acid (30 c.c.) was heated with zinc dust (6·0 g.) on a steam-bath. A stream of purified nitrogen was passed through the reaction vessel and thence into baryta water, but no carbon dioxide evolution was detected during reduction (2 hr.). The product precipitated by water was dissolved in ether and washed with aqueous sodium hydrogen carbonate and then with 1% aqueous sodium hydroxide. The sodium hydroxide-soluble fraction (0·5 g.) separated from methanol in an amorphous condition.

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The Chemistry of Extractives from Hardwoods. Part XXIV. A Saponin Constituent of Makoré* (Mimusops heckelii).

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From the ethanol extract of makoré, the wood of *Mimusops heckelii*, an amorphous saponin has been isolated which yields bassic acid on hydrolysis with aqueous-alcoholic acid. With aqueous acid a monoglucoside of bassic acid is obtained. Also present in the aqueous-alcoholic acid hydrolysate are D(?)-glucose, L-rhamnose, and D-xylose in the molar ratio of 1 : 2 : 2 to one molecule of triterpene. The saponin contains a sulphato-ester group, and there is evidence that this constituent is attached to the 6-position of the glucose residue.

Mimusops heckelii (family, *Sapotaceae*), a large tree occurring in the forests of West Africa, produces a resistant wood commonly termed makoré which in colour and texture superficially resembles mahogany. Apart from a quantitative estimation of its pentosan, cellulose, and lignin contents by Marmasse (Association colonies-sciences et comité national des bois coloniaux, Paris, 1931, *Chem. Abs.*, 1932, **26**, 3281), no chemical examination of the heartwood has been reported. It is, however, readily procured from commercial sources and in a further investigation of the timber the nature of some of its principal extractable constituents has been determined. Two distinct samples of makoré were purchased, as well as a quantity of wood marketed as balata—a description usually applied to a related species of West Indian origin, *viz.*, *M. balata*—but on examination at the D.S.I.R. Forest Products Research Laboratory, all three were found to be derived from *M. heckelii*, and, when treated with solvents, each afforded approximately equal quantities of similar products.

By successive extractions of the granulated wood with boiling light petroleum and with ether, comparatively small amounts of semi-solid substances were isolated and these were not further examined. Refluxing the wood with ethanol then yielded a viscous solution from which a solid was slowly deposited. This was purified by dissolution in water and treatment with lead acetate to precipitate tannins. Removal of soluble lead with hydrogen sulphide and evaporation, an operation which was complicated by foaming, yielded the friable colourless saponin; with a further crop of inferior quality obtained by concentrating the original alcoholic extract and processing in the manner already indicated, the yield amounted to 3% of the wood.

The product could not be obtained crystalline, and when incinerated it left an ash containing sodium, magnesium, and sulphate ions. Zeisel determinations indicated the presence of a persistent alkoxy-content, but in view of the purification of the saponin through alcohol it is uncertain whether this constituent is an integral part of the molecule. An aqueous solution of the saponin gave no sulphate reaction, but positive sulphate tests were obtained after short hydrolysis. The action of boiling aqueous-alcoholic mineral acid caused the precipitation of bassic acid, $C_{30}H_{46}O_5$, already shown by Heywood and Kon (*J.*, 1940, 713) to be present in the seeds of several plants belonging to the family *Sapotaceae*, including certain *Bassia* and *Mimusops* species. Its identity was confirmed by the preparation of the known methyl ester, *iso*propylidene derivative, and bromo-lactone.

Monosaccharides were detected in the aqueous-alcoholic hydrolysate from which the triterpene had been collected. By means of paper chromatography (Partridge, *Biochem. J.*, 1948, **42**, 239) the presence of glucose, rhamnose, and xylose was established. Subsequently, crystals of L-rhamnose monohydrate separated from the concentrated solution, and the preparation of L-rhamnose benzoylhydrazone and of di-*O*-benzylidene-D-xylose dimethyl acetal gave further evidence of their identity.

Hydrolysis of the saponin with *aqueous* mineral acid gave a crystalline prosapogenin consisting of bassic acid monoglucoside, which was resolved into its constituents by heating it with aqueous-ethanolic acid.

* Part XXIII, preceding paper.

Indications of the point of attachment of the sulphato-group were obtained by alkali treatment of the saponin followed by hydrolysis under acid conditions. The resulting mixed carbohydrates were examined chromatographically whereupon a fourth product was detected. From its higher R_F value this was identified as an anhydro-sugar, and direct comparison with 3 : 6-anhydro-D-glucose prepared from a specimen of methyl 3 : 5-anhydro-D-glucoside, kindly supplied by Professor M. Stacey, gave conclusive proof of its constitution. It therefore follows (cf. Peat, *Adv. Carbohydrate Chem.*, 1948, **2**, 38) that the sulphato-group is attached to the 6-position of the glucose unit. The acidic functions of the saponin are neutralised in the natural product, as is shown by the pH of its solution and by the presence of sodium and magnesium ions in the purified substance. The saponin-acid was obtained by precipitation of a solution of the natural material with basic lead acetate, the resulting lead salt being dissolved in aqueous acetic acid and freed from lead by passage through a column of ion-exchange resin.

Many experiments were made to ascertain the homogeneity of the saponin, *e.g.*, by dialysis and by chromatography. Analysis of the fractions thus obtained invariably showed the presence of glucose, rhamnose, and xylose in each—as far as could be estimated visually, in approximately the same relative proportions. All fractions also liberated sulphate ions on alkali treatment.

The relative amounts of the three sugars in the saponin were determined by the paper chromatography procedure of Flood, Hirst, and Jones (*J.*, 1948, 1679). It was necessary to use aqueous-ethanolic acid for the hydrolysis, afterwards neutralising the solution with an ion-exchange resin. The sugars were then separated and estimated by the Somogyi copper reagent (Flood *et al.*, *loc. cit.*). From the percentage of sulphur present in the saponin an estimate of the sulphato-groups was possible. The combined results suggest that the saponin contains one molecule of triterpene, one of glucose, two of rhamnose, two of xylose, and one sulphato-ester group. It cannot, of course, be supposed with any certainty that the saponin is a single chemical entity; nevertheless, the inability of chromatographic techniques to resolve it into different fractions, and the approximate whole-number ratio of the constituent parts, imply that if more than one compound is present all are of very similar composition. It is of interest to compare these results with those of investigations by Van der Haar (*Rec. Trav. chim.*, 1929, **48**, 1155, 1166) on the bassic acid saponins of *M. elengi* and *Achras sapota*, which show that arabinose, rhamnose, and glucose are present in the molecular ratio of approximately 2 : 2 : 1.

Information on the distribution of the carbohydrate residues was sought by the method of methylation, using methyl sulphate–aqueous sodium hydroxide followed by methyl iodide–methanol–silver oxide. The amorphous product was then hydrolysed and the triterpene fraction esterified with diazomethane. Treatment with benzene left a crystalline solid, $C_{30}H_{44}O_3(OMe)_2$, insoluble in alcoholic alkali and therefore regarded as a mono-methyl triterpene ester. The benzene solution contained a non-crystalline material, obtained by distillation in a high vacuum as a glass, which was isomeric with the less soluble product $C_{32}H_{50}O_3$. One triterpenoid alcoholic group is therefore unsubstituted in the original saponins, but owing to the possible operation of steric factors it does not necessarily follow that both remaining hydroxyl groups are glycosidically linked in the parent compound.

Experimental

Extraction of the Saponin from Mahoré.—Powdered heartwood of *Mimusops hechelii* (3 kg.) was extracted with boiling light petroleum (b. p. 60—80°) for 12 hr. When the solvent was evaporated a soft orange-yellow wax (12·3 g., 0·4%) remained. Afterwards, similar treatment with ether gave a red-brown wax (4 g., 0·13%). Thereafter, only ether was used for the preliminary treatment. The wood was then extracted for several hours with boiling ethanol (8 l.), and the dark red solution left in the refrigerator for 24 hr. The brown solid (72 g.) then deposited was collected and thoroughly washed with cold alcohol, care being taken to minimise exposure of the very deliquescent material to the air. However, after being washed with ether and dried in a vacuum-desiccator it formed a moisture-stable powder.

A solution of the crude product in hot water was, after filtration, treated with a saturated solution of lead acetate until precipitation was complete. The mixture was filtered and the last traces of tannins removed by boiling the filtrate with a small quantity of litharge insufficient for complete neutralisation of the acetic acid liberated during the precipitation. Excess of lead was removed as sulphide, its separation being assisted by the addition of charcoal and by filtration through diatomaceous earth. The colourless solution was evaporated to dryness with as much reduction in pressure as was possible without excessive frothing. Dissolution of the residue in absolute methanol removed insoluble inorganic matter (*ca.* 1 g.), and by evaporation the saponin was recovered as a white, friable amorphous solid (34 g.). When further purified by separation from a hot saturated solution in ethanol it was dried for analysis *in vacuo* at room temperature (Found: C, 46·2, 46·7; H, 7·4, 7·3; S, 1·9, 2·0; OMe, 2·0, 1·7; Ash, 3·4, 3·1. $C_{59}H_{98}O_{39}SNa,10H_2O$ requires C, 47·2; H, 7·5; S, 2·1; OMe, 2·1%).

By evaporation of the original alcoholic solution, finally to dryness in an open vessel, a dark resinous powder (150 g.) was obtained, from which by extraction with hot water and purification by the addition of lead acetate in the manner already outlined, an additional quantity of the *glycoside* (55 g.) was recovered as a light brown powder. Although less pure than the first fraction, the product was suitable for the investigation of its hydrolysis products.

The saponin, decomp. 180° to 220° according to the rate of heating, was very readily soluble in water and methanol, but much less soluble in ethyl alcohol. It showed no reaction with Fehling's solution or ammoniacal silver nitrate, and gave a precipitate with barium chloride only after hydrolysis with acids or alkalis.

Bassic Acid.—The saponin (50 g.) in aqueous-ethanolic (1 : 1) 2N-sulphuric acid (300 c.c.) was boiled under reflux on a steam-bath for 12 hr. The brown solid which separated from the hot solution was collected from the cooled mixture and washed with 50% aqueous ethanol and finally digested with absolute ethanol. The sandy residue consisted of bassic acid (7 g., 14%) which crystallised (charcoal) either from aqueous acetic acid as the monohydrate, needles, m. p. 290° (decomp.) (Found: C, 71·7; H, 9·7. Calc. for $C_{30}H_{46}O_5,H_2O$: C, 71·3; H, 9·5%), or from aqueous 2-ethoxyethanol as anhydrous prisms, m. p. 320° (decomp.), $[\alpha]_D$ +79° (in pyridine) (Found: C, 74·3; H, 9·5. Calc. for $C_{30}H_{46}O_5$: C, 74·0; H, 9·5%). Heywood, Kon, and Ware (*J.*, 1939, 1124) give for bassic acid, m. p. 320°, $[\alpha]_D$ +82·4—82·9°.

The methyl ester prepared with diazomethane crystallised from aqueous methanol as needles, m. p. 212°, $[\alpha]_D$ +56° (in MeOH) (Found: C, 74·1; 74·2; H, 9·6, 9·8; OMe, 6·2. Calc. for $C_{31}H_{48}O_5$: C, 74·4; H, 9·7; OMe, 6·2%). Heywood *et al.* (*loc. cit.*) give for α-methyl bassate, m. p. 213°, $[\alpha]_D$ +64° and for β-methyl bassate, m. p. 210°, $[\alpha]_D$ +55·5°.

The characteristic *iso*propylidene derivative of the methyl ester was prepared in acetone with a trace of hydrochloric acid, forming flat prisms, m. p. 206° (lit., 206°) (Found: C, 75·1, 75·3; H, 9·3, 9·5; OMe, 5·4. Calc. for $C_{34}H_{52}O_5$: C, 75·4; H, 9·7; OMe, 5·8%). The acid with bromine in acetic acid gave the bromo-lactone, colourless needles (from aqueous acetic acid), m. p. 220° (lit., 220°) (Found: C, 63·1; H, 7·7; Br, 13·4. Calc. for $C_{30}H_{45}O_5Br$: C, 63·7; H, 8·0; Br, 14·1%).

Bassic Acid Glucoside.—The saponin (5 g.) was hydrolysed on a steam-bath with 2N-sulphuric acid (25 c.c.) for 5 hr., the original gelatinous precipitate having then coagulated. The solid was collected and washed repeatedly with hot water to remove mineral acid and finally dried (desiccator). The pale yellow powdery product (2 g.) was taken up in cold ethanol (25 c.c.), and the solution filtered and allowed to evaporate at room temperature to a third of its bulk; the crystalline deposit (0·5 g.) of the *monoglucoside* then readily crystallised from aqueous ethanol as needles, m. p. 225°, $[\alpha]_D$ +40° (*c*, 0·37 in EtOH) (Found: C, 66·9; H, 9·0. $C_{34}H_{56}O_{10}$ requires C, 66·7; H, 8·6%). The prosapogenin gave a crystalline sodium salt from aqueous-alcoholic sodium hydroxide, but the acetate was amorphous. The *methyl ester*, prepared with diazomethane, crystallised from aqueous methanol as long colourless needles, m. p. 141—142°, $[\alpha]_D$ +45° (*c*, 0·64 in EtOH) (Found: C, 66·8; H, 9·1; OMe, 5·1. $C_{37}H_{58}O_{10}$ requires C, 67·1; H, 8·8; OMe, 4·7%).

Treatment of the prosapogenin with 4N-sulphuric acid at 100° (sealed tube) for 48 hr. gave bassic acid and D-glucose (identified by chromatography on paper) as its sole hydrolysis products.

Carbohydrate Constituents of the Saponin.—(a) *Identification.* The soluble hydrolysate and washings from the aqueous-alcoholic hydrolysis of the saponin were neutralised with barium carbonate, and the mixture was filtered. The filtrate was evaporated under reduced pressure and the residue redissolved in boiling methanol. After removal of a small amount of insoluble material, evaporation of the filtrate gave the sugars as a syrupy mass. Paper partition chromatography in butanol–water, butanol–ethanol–water (4 : 1 : 5), and butanol–acetic acid–

water (4 : 1 : 5) gave three spots identified by the R_F values and by direct comparison with authentic specimens as being due to glucose, xylose, and rhamnose.

A portion of the syrupy sugar mixture slowly deposited L-rhamnose monohydrate, m. p. 94°, $[\alpha]_D$ +8·3° (in H_2O) (Found : C, 39·3; H, 7·8. Calc. for $C_6H_{12}O_5,H_2O$: C, 39·6; H, 7·7%). This was further characterised as the benzoylhydrazone (Hirst, Jones, and Wood, *J.*, 1947, 1048), m. p. and mixed m. p. 180°. The crude sugar mixture with benzaldehyde and hydrogen chloride in methanol slowly deposited di-*O*-benzylidene-D-xylose dimethyl acetal (Breddy and Jones, *J.*, 1945, 738), m. p. and mixed m. p. 211° (Found : C, 67·4; H, 6·5; OMe, 15·9. Calc. for $C_{27}H_{34}O_6$: C, 67·7; H, 6·5; 2OMe, 16·7%).

(b) *Estimation.* Samples of the saponin of *ca.* 0·1 g. were hydrolysed in 2N-hydrochloric acid in 30% aqueous ethanol in a sealed tube for 8 hr. After neutralisation of the cooled solution with a basic ion-exchange resin (Amberlite IR.4B) the relative proportions of the sugars present were determined by the method of Flood *et al.* (*loc. cit.*). The mean of three determinations gave the molecular ratios of glucose : xylose : rhamnose to be 1 : 2·1 : 2·0.

Alkali Hydrolysis of the Saponin.—The saponin (1 g.) was hydrolysed with boiling saturated aqueous barium hydroxide for 1 hr., and the solution so obtained was acidified with sulphuric acid and then neutralised with barium carbonate. The filtrate from this operation was examined for the presence of sugars by paper chromatography in butanol–ethanol–water (4 : 1 : 5) for development. In addition to spots due to glucose, xylose, and rhamnose, aniline phthalate revealed a fourth faster-running spot identified by its position on the paper compared with that of an authentic specimen as due to 3 : 6-anhydro-D(?)-glucose.

The Saponin-acid.—A solution of the saponin salt (5 g.) in water (25 c.c.) was treated with an excess of saturated basic lead acetate. The lead salt of the saponin was collected and thoroughly washed and then dissolved in dilute acetic acid, and the solution freed from lead by passage down a column of acid ion-exchange resin (Zeocarb 215). The lead-free eluate was evaporated at 30—40° by drawing a stream of dust-free air over the surface and finally in a vacuum-desiccator to give a pale yellow glassy powder, very soluble in water.

Fractionation of the Saponin.—(a) *Dialysis.* The saponin acid (5 g.) was dissolved in water (50 c.c.) and the solution was placed in a seamless "Visking" tube and rotated slowly in a beaker containing water (350 c.c.). A total of 12 fractions were collected, the first 5 after 12 hr. and the remainder after 24 hr. The first 2 fractions after evaporation gave coloured gums, the remainder giving colourless products. The twelve fractions contained a total of 3·9 g. of solid, each fraction giving sulphate on brief alkali hydrolysis, and on acid hydrolysis bassic acid and a solution containing glucose, xylose, and rhamnose, the proportions, so far as could be estimated visually from the size and intensity of the spots obtained on paper chromatography, being the same in each case.

(b) *Chromatography.* Large-scale paper chromatography of the saponin acid by Novellie's method (*Nature*, 1952, **169**, 672) on wide strips of paper for prolonged periods during which the developing liquid (butanol–methanol–water, 4 : 1 : 5) was allowed to drip from the end of the paper gave a chromatogram, a test strip from the edge of which was developed by one of three methods, namely (i) thermal preferential charring of the saponin at 200°, (ii) preferential charring of the saponin by concentrated sulphuric acid, and (iii) spraying with bromocresol-green. In every case the saponin was spread over a considerable length of paper, but only in one of several experiments was any positive separation indicated. Horizontal strips were cut from the main chromatogram at places spaced along the area occupied by the saponin and these were extracted completely with water. Each fraction was thus shown to give sulphate on alkaline hydrolysis and glucose, xylose, and rhamnose on acid hydrolysis.

Methylation of the Saponin.—The saponin (5 g.) in water (10 c.c.) was methylated at 70° by the dropwise addition of aqueous sodium hydroxide (25 g. of 30%) and methyl sulphate (28·5 g.) at such a rate that the solution remained alkaline. During the reaction the product separated as a rubbery mass which was collected and washed free from alkali with cold saturated sodium sulphate solution. The dried product was further treated in boiling methanol for 5 hr. with silver oxide (5 g.) and methyl iodide (10 c.c.), this being followed by the addition of more silver oxide (5 g.) and methyl iodide (10 c.c.) and further heating for 15 hr. Silver salts were then removed and the filtrate was evaporated. The residue was dissolved in boiling methyl iodide (30 c.c.), silver oxide (10 g.) was added, and heating continued for 48 hr., a further portion of silver oxide (10 g.) being added after 24 hr. The silver salts were then removed and the filtrate was evaporated to give the methylated saponin as a pale yellow friable amorphous solid (3·3 g.).

Methyl O-Monomethylbassate.—The methylated saponin (3·3 g.) was hydrolysed by boiling with aqueous-methanolic (1 : 1) 2N-hydrochloric acid (50 c.c.) for 4 hr. Evaporation of the methanol

led to the separation of the aglycone which was collected and further hydrolysed in methanol (35 c.c.) with boiling 6N-hydrochloric acid (15 c.c.) for 9 hr. The aglycone isolated after evaporation of the methanol was then methylated with diazomethane, giving *methyl O-methylbassate* which separated from benzene in colourless needles (0·13 g.), m. p. 245—246° (Found: C, 74·7; H, 9·2; OMe, 7·3. $C_{32}H_{56}O_5$ requires C, 74·8; H, 9·7; 2OMe, 10·7%). The ester was not readily hydrolysed by 10% methanolic potassium hydroxide and did not react under the conditions in which methyl bassate gives an *iso*propylidene derivative.

High-vacuum distillation of the residue from the benzene mother-liquors of the above ester gave a glassy non-crystallisable solid, b. p. 200—210° (air-bath)/10^{-4} mm., apparently isomeric with the crystalline ester (Found: C, 74·8; H, 9·6%). It failed to give a crystalline *iso*propylidene derivative with acetone–hydrochloric acid.

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Experiments on Halogenated Ketones. The Conversion of 1-*Bromo*-1 : 3-*diphenylpropan*-2-*one into* 1-*Phenylindan*-2-*one.*

By A. C. B. SMITH and WALTER WILSON.

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1-Bromo-1 : 3-diphenylpropan-2-one undergoes Friedel–Crafts type reactions in the presence of aluminium chloride; with benzene it affords some 1 : 1 : 3-triphenylpropan-2-one (19%). In the absence of benzene, intramolecular reaction yields 1-phenylindan-2-one (80%); 1-bromo-3-phenylpropan-2-one is not cyclised thus. In the presence of hydrogen bromide, 1-bromo-3-phenylpropan-2-one rearranges to 1-bromo-1-phenylpropan-2-one; each isomer forms a distinctive 2-aminothiazole derivative when treated with thiourea. β-Bromo-propiophenone, which is believed to be identical with a product described by Grignard and Perrichon as 1-bromo-3-phenylpropan-2-one, with semicarbazide gives an unstable semicarbazone which cyclises to a carbamoylpyrazoline; the latter is synthesised by an alternative method.

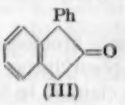
α-HALOGENATED ketones often undergo Friedel–Crafts reactions with aromatic compounds; in particular, ketones (I) with benzene and aluminium chloride have given the *gem*-diphenyl compounds (II) [R = Me: Ruggli, Dahn, and Wegmann, *Helv. Chim. Acta*, 1946, **29**, 113; Schultz and Mickey, *Org. Synth.*, 1949, **29**, 38; R = Ph (chloroketone): MacKenzie and Lesslie, *Ber.*, 1928, **61**, 158], and α-alkyl *gem*-diphenyl ketones have been obtained similarly (Schultz, Bicking, Mickey, and Crossley, *J. Amer. Chem. Soc.*, 1953, **75**, 1072).

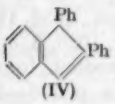
Treatment of crude 1-bromo-1 : 3-diphenylpropan-2-one (I; R = CH_2Ph) with benzene and aluminium chloride gave a mixture from which 1 : 1 : 3-triphenylacetone (II; R = CH_2Ph) was isolated in only 19% yield. The product was identified by the oxime and by comparison with an authentic sample made by rearrangement of 1 : 2 : 3-triphenylpropane-1 : 2-diol (Orékhoff, *Bull. Soc. chim. France*, 1919, **25**, 108). It seemed probable that the low yield of triphenylacetone was due to an intramolecular condensation affording 1-phenylindan-2-one (III) and its transformation products. Indan-2-ones are relatively uncommon, but Kohler and Weiner (*J. Amer. Chem. Soc.*, 1934, **56**, 434) obtained 1-methyl-1 : 3-diphenylindan-2-one by heating 1-hydroxy-1-methyl-1 : 3 : 3-triphenylpropan-2-one with hydriodic acid; this appears to be the only recorded example of the formation of an indan-2-one by a reaction formally analogous to (I) ⟶ (III).

Attempts were therefore made to cyclise α′-bromo-α-phenylalkyl ketones to indan-2-ones. Bromination of 1 : 3-diphenylacetone by an improved method afforded crystalline 1-bromo-1 : 3-diphenylpropan-2-one (I; R = CH_2Ph) which was characterised by conversion into 2-amino-4-benzyl-5-phenylthiazole, and into the corresponding anilino-ketone

(McGeoch and Stevens, *J.*, 1935, 1032; Julian, Meyer, Magnani, and Cole, *J. Amer. Chem. Soc.*, 1945, **67**, 1203). Francis (*J.*, 1899, 865) claimed to have obtained the anilino-ketone anil (m. p. 127·5°; hydrochloride, m. p. 176°) from the bromo-ketone and aniline. There is little doubt that Francis's product was the anilino-ketone, which has m. p. 127—129°

(I) Ph·CHBr·COR $Ph_2CH{\cdot}COR$ (II)


(III)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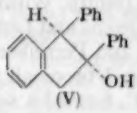
(V)

and forms a hydrochloride m. p. 172—174°. We obtained no evidence of anil formation; furthermore, the Bischler mechanism for indole synthesis which postulates intermediate anilino-ketone anils has been criticised recently (Crowther, Mann, and Purdie, *J.*, 1943, **58**; *Annual Reports*, 1946, **43**, 242). 1-Bromo-1 : 3-diphenylpropan-2-one and sodium iodide in acetone afforded the unstable α-iodo-ketone, which rapidly liberated iodine on warming or on ultraviolet irradiation in light petroleum solution. This bromo-ketone also condensed readily with 1 : 3-diphenylacetone in alkaline media, giving an unidentified compound $C_{30}H_{26}O_2$, m. p. 200—202°. 1-Bromo-1 : 3-diphenylpropan-2-one in presence of aluminium chloride in cold carbon disulphide gave 1-phenylindan-2-one (III), m. p. 51—53°, in 80% yield. The indanone formed a 2 : 4-dinitrophenylhydrazone (m. p. 199°) and a semicarbazone (m. p. 200—202°), reduced ammoniacal silver nitrate solutions, and slowly dissolved in cold aqueous sodium hydroxide. The indanone somewhat resembles 1 : 2-diphenylpropaldehyde for which Burton and Shoppee (*J.*, 1937, 546) give m. p. 54°, two 2 : 4-dinithrophenylhydrazones of m. p. 148—152° and 199°, semicarbazone of m. p. 125° (see also Ramart-Lucas and Salmon-Lecagneur, *Bull. Soc. chim. France*, 1932, **51**, 1084, who made a semicarbazone, m. p. 120—121°). Although 1-bromo-1 : 3-diphenylpropan-2-one might have given 1 : 2-diphenylpropaldehyde by a type of retro-Danilov rearrangement, this structure was excluded because the product did not afford αβ-diphenylpropionic acid on oxidation with silver oxide (cf. Ramart-Lucas and Salmon-Lecagneur, *loc. cit.*). Confirmation of the 1-phenylindan-2-one structure was obtained by treatment with phenylmagnesium bromide and dehydration of the intermediate alcohol [not isolated, but presumably the *cis*-diphenyl compound (V)] to 1 : 2-diphenylindene (IV), which was identical with a specimen made from 1 : 2 : 3-triphenylpropane-1 : 2-diol (Orékhoff and Tiffeneau, *Bull. Soc. chim. France*, 1922, **31**, 253; cf. McKenzie and Roger, *Ber.*, 1929, **62**, 284). By a similar sequence of reactions, Koelsch and Johnson (*J. Org. Chem.*, 1941, **6**, 534) converted 2-phenylindan-1-one into 2 : 3-diphenylindene. All the indane derivatives encountered in our experiments give the expected intense blue or green solutions in concentrated sulphuric acid. The reducing properties and alkali-solubility (with ring scission) of 1-phenylindan-2-one are a little unexpected, but recall the behaviour of some other indanones (*e.g.*, 2-phenylindan-1-one; von Miller and Rohde, *Ber.*, 1892, **25**, 2095; von Auwers and Auffenberg, *Ber.*, 1919, **52**, 92). Attempts were made unsuccessfully to convert 1-phenylindan-2-one into the known 1-phenylindane-2 : 3-dione or its dioxime (Pfeiffer and de Waal, *Annalen*, 1935, **520**, 185; Koelsch, *J. Amer. Chem. Soc.*, 1936, **58**, 1321).

(VI) $Ph{\cdot}CH_2{\cdot}CO{\cdot}CH_2Br$ Ph·CHBr·COMe (VII)

For the conversion of α-bromo-α′-phenylalkyl ketones into indan-2-ones, activation of the bromine by a suitable α-substituent appears to be necessary Thus, no indanone was obtained from 1-bromo-3-phenylpropan-2-one (VI), which was recovered unchanged after treatment with aluminium chloride. The preparation of 1-bromo-3-phenylpropan-2-one (VI) from phenylacetyl chloride and diazomethane followed by treatment with hydrogen bromide (Catch, Elliott, Hey, and Jones, *J.*, 1948, 287; cf. Diesbach, Capponi, and Farquet, *Helv. Chim. Acta*, 1949, **32**, 1226) was attended by unexpected complications, as the bromomethyl ketone (VI) was found to rearrange to 1-bromo-1-phenylpropan-2-one (VII) in the presence of hydrogen bromide. The latter bromo-ketone was also obtained

by direct bromination of phenylacetone. The two isomeric bromo-ketones were characterised by treating them with thiourea, which gave thiazole derivatives having the expected light-absorption properties. A preliminary account of the rearrangement of 1-bromo-3-phenylpropan-1-one has already been given (Smith, Wilson, and Woodger, *Chem. and Ind.*, 1954, 309); the light-absorption of thiazoles will be discussed in a forthcoming communication. The above rearrangement is believed to occur by debromination–bromination (Smith, Wilson, and Woodger, *loc. cit.*; Newman, *J. Amer. Chem. Soc.*, 1951, **73**, 4993; Stevens and Lenk, *J. Org. Chem.*, 1954, **19**, 528).

Grignard and Perrichon (*Ann. Chim.*, 1926, **5**, 5) obtained several bromomethyl ketones by hydrating 1-bromoalkynes. The product from 1-bromo-3-phenylprop-1-yne (VIII) had m. p. 58°, formed a semicarbazone m. p. 225—230°, and was claimed to be 1-bromo-3-phenylpropan-2-one (VI). However, the calculated percentage composition and " found " analytical figures are incorrect, and no analysis is given for the semicarbazone. We believe that Grignard and Perrichon's product was actually β-bromopropiophenone (X), which has m. p. 58° (Foreman and McElvain, *J. Amer. Chem. Soc.*, 1940, **62**, 1435), a rearrangement (*e.g.*, VIII ⟶ IX) having taken place during their synthesis. Little progress was made in repeating their reaction, as the intermediate benzylacetylene was not easily obtained and isomerised or polymerised readily. We prepared a sample of β-bromopropiophenone, m. p. 58°, by a method used for the corresponding chloro-ketone (Kohler, *Amer. Chem. J.*, 1909, **42**, 389), and studied its reaction with semicarbazide. No compound of m. p. 225—230° was obtained; however, Grignard and Perrichon's unanalysed " semicarbazone " of this m. p. may well have been impure hydrazodicarboxyamide, for which various m. p.s from 245° to 270° have been quoted. Authentic β-bromopropiophenone with semicarbazide under mild conditions yielded an unstable semicarbazone, m. p. 130°; at higher temperatures cyclisation occurred, and 1-carbamoyl-3-phenyl-Δ^2-pyrazoline (XI; R = $CO{\cdot}NH_2$) was obtained (cf. Maire, *Bull. Soc. chim. France*, 1908, **3**, 272). The structure of this product was confirmed by an independent preparation from 3-phenyl-Δ^2-pyrazoline (XI; R = H) and cyanic acid (cf. von Auwers and Heimke, *Annalen*, 1927, **458**, 194).

$Ph{\cdot}CH_2{\cdot}C{\equiv}C{\cdot}Br$ (VIII) $\quad Ph{\cdot}C{\equiv}C{\cdot}CH_2Br$ (IX) $\quad Ph{\cdot}CO{\cdot}CH_2{\cdot}CH_2Br$ (X)

(XI)

Experimental

Reaction of 1-*Bromo*-1 : 3-*diphenylpropane*-2-*one with Benzene.*—Bromine (16 g.) was added dropwise during 90 min. to a stirred solution of 1 : 3-diphenylpropan-2-one (21 g.) in dry, thiophen-free benzene (75 c.c.) at 20°. A stream of dry nitrogen was then blown through the solution for 2 hr. to expel hydrogen bromide. The resulting benzene solution of crude 1-bromo-1 : 3-diphenylpropan-2-one was dropped during 1 hr. into a gently refluxing and stirred mixture of pure benzene (60 c.c.) and powdered aluminium chloride (27 g.). The mixture was refluxed for a further hour, cooled, and treated with ice (175 g.) and concentrated hydrochloric acid (40 c.c.), and the organic layer was separated, washed with sodium hydrogen carbonate solution, and dried (Na_2SO_4). Distillation afforded a main fraction (19·5 g.), b. p. 90—180°/0·1 mm. Further distillation gave unidentified oils and a fraction, b. p. 160—180°/0·06 mm., which solidified; recrystallisation from ethanol afforded 1 : 1 : 3-triphenylpropan-2-one (5·3 g., 17%), m. p. 79—81°, raised to 80—81° on a further crystallisation. The m. p. was not depressed by admixture with a specimen, m. p. 81—82°, prepared from 1 : 2 : 3-triphenylpropane-1 : 2-diol and concentrated sulphuric acid (Orékhoff, *loc. cit.*). (The ketone is most conveniently obtained by the latter method.) The oxime, obtained in pyridine, had m. p. 133—135° (Orékhoff, *loc. cit.*, gives m. p. 134—135°).

1-*Bromo*-1 : 3-*diphenylpropan*-2-*one.*—Bromine (7·7 c.c.) was added during 1 hr. to a stirred mixture of 1 : 3-diphenylpropan-2-one (31·5 g.), carbon disulphide (150 c.c.), and finely powdered calcium carbonate (15 g.). The mixture was stirred for a further hour, then treated with water, and the carbon disulphide layer dried and evaporated. The residue (42 g., 97%), recrystallised twice from light petroleum (b. p. 40—60°), gave the bromo-ketone (27 g., 62%) as colourless needles, m. p. 45—47° (Bourcart, *Ber.*, 1889, **22**, 1368, gives m. p. 43—44°; Francis, *J.*, 1899,

865, m. p. 49°; and Veksler, *J. Gen. Chem., U.S.S.R.* 1950, **20**, 1289, m. p. 48—48·5°). Distillation of the bromo-ketone is not recommended.

2-Amino-4-benzyl-5-phenylthiazole.—The above bromo-ketone (2·9 g.), thiourea (0·76 g.), and ethanol (25 c.c.) were refluxed for 3 hr. The *thiazole hydrobromide* (59%), m. p. 215—218° (with previous sintering), was recrystallised from ethanol (Found: S, 8·85. $C_{16}H_{15}N_2SBr$ requires S, 9·25%). The free base had m. p. 143—144° (King and Hlavacek, *J. Amer. Chem. Soc.*, 1950, **72**, 3722, give m. p. 139—140°).

1-Anilino-1 : 3-diphenylpropan-2-one.—Reaction of aniline (2 mols.) with the above bromo-ketone for ½ hr. afforded the anilino-ketone (97%), m. p. 127—129° (McGeoch and Stevens, *loc. cit.* give m. p. 125°). The *hydrochloride*, m. p. 172—174°, obtained from the base and alcoholic hydrogen chloride (Found: N, 4·1. $C_{21}H_{19}ON,HCl$ requires N, 4·15%), was decomposed by hot ethanol, and the free base crystallised on cooling. The anilino-ketone was the sole product from several reactions carried out at higher temperatures.

Condensation of 1-Bromo-1 : 3-diphenylpropan-2-one with 1 : 3-Diphenylpropan-2-one.—A mixture of the bromo-ketone (210 mg.), ketone (150 mg.), and ethanol (5 c.c.) was treated with one drop of 10N-sodium hydroxide. The solid *substance* (50 mg.) produced had m. p. 200—202° (Found: C, 86·2, 86·1; H, 6·3, 6·3. $C_{30}H_{26}O_2$ requires C, 86·1; H, 6·25%).

Reaction of 1-Bromo-1 : 3-diphenylpropan-2-one with Sodium Iodide.—The bromo-ketone (2·9 g.), sodium iodide (1·5 g.), and acetone (110 c.c.) were mixed and left at 20° for about ½ hr., then poured into water. The solid (3 g.; m. p. 70—72°) obtained was recrystallised carefully from light petroleum (b. p. 40—60°). However, some decomposition occurred, and the iodo-ketone, m. p. 74—76°, was not obtained pure (Found: I, 28·65. Calc. for $C_{15}H_{13}OI$: I, 37·8%). The impure iodo-ketone (157 mg.) was dissolved in light petroleum (b. p. 40—60°) in a quartz flask and irradiated with an ultra-violet lamp for 5 hr. Thiosulphate titration indicated that 59% of the iodine had been liberated. Refluxing a solution of the iodo-ketone in light petroleum (b.p. 40—60°) in diffused daylight for 5 hr. liberated 15% of the iodine.

1-Phenylindan-2-one.—A solution of recrystallised 1-bromo-1 : 3-diphenylpropan-2-one (8·7 g.) in carbon disulphide (60 c.c.) was added during 35 min. to a cold stirred mixture of carbon disulphide (30 c.c.) and powdered aluminium chloride (8·1 g.). The mixture was then stirred for a further 75 min., again at room temperature, and treated with cold dilute hydrochloric acid. The carbon disulphide layer was separated. Distillation afforded an oil, b. p. 130—135°/0·2 mm. (5 g., 80%), which solidified; recrystallisation from light petroleum (b. p. 40—60°), yielded *1-phenylindan-2-one* as large colourless prisms, m. p. 51—53° (Found: C, 86·3; H, 5·9. $C_{15}H_{12}O$ requires C, 86·5; H, 5·8%). The *2 : 4-dinitrophenylhydrazone*, m. p. 199° (decomp.), was orange-yellow and almost insoluble in ethanol (Found: C, 64·7; H, 4·45; N, 14·0. $C_{21}H_{16}O_4N_4$ requires C, 64·95; H, 4·15; N, 14·45%). The *semicarbazone* (obtained by using semicarbazide hydrochloride in aqueous ethanol) had m. p. 200—202° (with previous sintering) (Found: N, 15·2. $C_{16}H_{15}ON_3$ requires N, 15·85%). The indanone reacted readily with nitrous acid (*n*-butyl nitrite and aqueous hydrochloric acid in ethanol); the product was a brownish-yellow solid, crystallising as a pinkish powder, m. p. 157° (approx.), from ethanol (Found: C, 84·3; H, 4·9; N, 0·75%), which gave an amorphous product with hydroxylamine acetate. The indanone reacted vigorously with *p*-nitrosodimethylaniline in ethanol; no crystalline product was obtained from the dark green solution, and 3-phenylindane-1 : 2-dione was not formed when the product was boiled with aqueous hydrochloric acid. 1-Phenylindan-2-one was shaken overnight with moist silver oxide, suspended in ether; metallic silver was formed, together with an unidentified pink solid, m. p. 80° (indefinite), which was insoluble in aqueous sodium hydroxide, reduced ammoniacal silver nitrate, and gave a deep blue colour with concentrated sulphuric acid. The indanone slowly dissolved in aqueous sodium hydroxide, and on acidification an unidentified acid, m. p. 130°, was obtained. The indanone readily reduced ammoniacal silver nitrate solution, gave an intense green colour, changing to intense blue on warming, with concentrated sulphuric acid, and gave no derivative with benzaldehyde in acid or alkaline media.

1 : 2-Diphenylindene.—1-Phenylindan-2-one (200 mg.) in ether (2 c.c.) was added to a Grignard solution made from bromobenzene (800 mg.), magnesium (150 mg.), and ether (5 c.c.). When the vigorous reaction subsided the mixture was refluxed for 2 hr., cautiously treated with cold dilute hydrochloric acid, and steam-distilled to remove ether and traces of diphenyl and bromobenzene. Ether-extraction of the residue gave an oil which was dissolved in glacial acetic acid (5 c.c.) containing water (2 drops) and concentrated sulphuric acid (0·5 c.c.), warmed at 75° for only 5 min., then cooled to 15°. The crystalline product (100 mg.; m. p. 150—155°) was filtered off and washed thoroughly with water. Recrystallisation from benzene–light petroleum

(b. p. 40—60°) afforded 1 : 2-diphenylindene, as needles, m. p. 172—174°, not depressed on admixture with a specimen (m. p. 173—175°) prepared from 1 : 2 : 3-triphenylpropane-1 : 2-diol and acetyl chloride (Orékhoff and Tiffeneau; McKenzie and Roger, *locc. cit.*). The indene gave an intensely green solution in warm concentrated sulphuric acid.

1-Bromo-3-phenylpropan-2-one.—Phenylacetyl chloride was treated with diazomethane in pure ether, and dry hydrogen bromide passed into the mixture (cf. Catch, Elliott, Hey, and Jones, *loc. cit.*). The ether solution was immediately washed with dilute aqueous sodium hydrogen carbonate, dried, and distilled, to give the bromo-ketone, b. p. 88—90·5°/0·15 mm., m. p. 15—20°, n_D^{25} 1·5586 (Catch, Elliott, Hey, and Jones, *loc. cit.*, give b. p. 106°/0·2 mm., $n_D^{15·5}$ 1·5593). The bromo-ketone with thiourea in ethanol afforded 2-amino-4-benzylthiazole hydrobromide, m. p. 88—89° ($\lambda_{max.}$ 259 mμ, ε 7600 in acid ethanol); the free base had m. p. 93—94° (Libermann and Moyeux, *Bull. Soc. chim. France*, 1950, 301, give m. p. 96—97°). Semicarbazide hydrochloride (0·35 g.), the bromo-ketone (0·67 g.), and cold aqueous ethanol (10 c.c.) soon deposited a solid (0·65 g.; m. p. 136—137°); recrystallisation from ethanol gave the fairly stable *semicarbazone*, m. p. 137—138° (Found: Br, 30·0. $C_{10}H_{12}ON_3Br$ requires Br, 29·6%). Under similar conditions, 1-phenylpropan-2-one also formed a semicarbazone, but 1-bromo-1-phenylpropan-2-one and 1-bromo-1 : 3-diphenylpropan-2-one did not.

Attempted Cyclisation of 1-Bromo-3-phenylpropan-2-one.—The bromo-ketone (3·35 g.) in carbon disulphide (25 c.c.) was added during 1 hr. to a refluxing mixture of carbon disulphide (15 c.c.) and powdered aluminium chloride (4·25 g.). The mixture was stirred and refluxed for a further 1½ hr., then poured into cold dilute hydrochloric acid and worked up in the usual way. This gave unchanged bromo-ketone (3·25 g., 97%), b. p. 55—60°/0·01 mm., which gave a copious precipitate with alcoholic silver nitrate, and with semicarbazide hydrochloride in cold ethanol gave the semicarbazone (75% yield), m. p. and mixed m. p. 136—137°.

1-Bromo-1-phenylpropan-2-one.—(a) *From 1-phenylpropan-2-one.* Bromine (25 g.) was added with stirring to a solution of phenylacetone (20 g.) in benzene at 20° during 30 min. Hydrogen bromide was removed in a stream of nitrogen during 2 hr. The liquid was washed with water and distilled; the bromo-ketone (14·4 g., 45%) had b. p. 122—126°/8 mm. (Babichev, *Ukrain. Chem. J.*, 1950, **16**, 188, gives b. p. 122—123°/5 mm.). This bromo-ketone (5 g.), thiourea 1·7 g.), and ethanol (17 c.c.), refluxed for 3½ hr., gave *2-amino-4-methyl-5-phenylthiazole hydrobromide*, m. p. 213—215° (from ethanol), $\lambda_{max.}$ 281 mμ, (ε 12,900 in acid ethanol) (Found: C, 44·3; H, 4·1. $C_{10}H_{10}N_2S,HBr$ requires C, 44·3; H, 4·1%). The free base had m. p. 166—168° (Kopp, *Bull. Soc. chim. France*, 1950, 582, gives m. p. 164—166°).

(b) *By rearrangement of 1-bromo-3-phenylpropan-2-one.* 1-Bromo-3-phenylpropan-2-one (1·08 g.) was dissolved in undried ether (5 c.c.) containing 285 g. of dissolved hydrogen bromide per l. After being kept in the dark for 52 hr. the red-brown solution was diluted with ether (100 c.c.) washed with sodium hydrogen carbonate solution and water, then dried (Na_2SO_4). Removal of the solvent gave an oil (1·03 g.); this was refluxed with thiourea (0·37 g.) in ethanol (25 c.c.) for 3 hr.; the resulting solution (acidified) had pronounced light absorption at 278 mμ with an inflexion at 245 mμ. The ethanol was removed, and the solid product crystallised from ethanol–ether, affording impure 2-amino-4-methyl-5-phenylthiazole hydrobromide (0·76 g., 55%), m. p. 183—193°, raised to 215—217° on three further crystallisations. The m. p. was not depressed on admixture with the authentic hydrobromide, and the free base had m. p. 164—166°. In other experiments, the rearranged bromo-ketone was distilled; the product gave 2-amino-4-methyl-5-phenylthiazole with thiourea.

β-Bromopropiophenone (cf. Mannich and Heilner, *Ber.*, 1922, **55**, 360).—β-Dimethylaminopropiophenone hydrochloride was dissolved in water, and steam-distilled for several hours, a little quinol being added to the solution and to the distillate. Crude 1-phenylprop-2-en-1-one (67%) was isolated from the distillate by careful ether-extraction. This unsaturated ketone (1·93 g.) was immediately dissolved in anhydrous ether (20 c.c.) and ethereal hydrogen bromide (21 c.c. of a solution containing 90 g. of acid per l. of ether) added. After 20 hr. the ether was removed. The solid product (2·9 g., 92%) was recrystallised from light petroleum (b. p. 40—60°), to give β-bromopropiophenone (2·3 g., 73%) as white crystals, m. p. 57—59° (Foreman and McElvain, *J. Amer. Chem. Soc.*, 1940, **62**, 1435, give m. p. 58—59°).

Reaction of β-Bromopropiophenone with Semicarbazide.—(*a*) The bromo-ketone (520 mg.) was dissolved in cold ethanol (12 c.c.) containing water (2·5 c.c.), and semicarbazide hydrochloride (270 mg.) added. The mixture was shaken for 1 hr., then sodium acetate trihydrate (335 mg.) was added. After 12½ hr., the crystals were filtered off and washed with cold water, giving impure bromo-ketone semicarbazone (220 mg.), m. p. 130° (decomp., with previous sintering) (Found: N, 14·3. Calc. for $C_{10}H_{12}ON_3Br$: N, 15·55%). The compound

liberated hydrogen bromide on attempted recrystallisation. (*b*) The bromo-ketone (455 mg.) in ethanol (9·5 c.c.) and water (2 c.c.) was shaken with semicarbazide hydrochloride (240 mg.) at 20° for 1½ hr. Sodium acetate trihydrate (290 mg.) was added, and the solution refluxed for 2 hr. The mixture was evaporated to dryness and the residue extracted with benzene. Evaporation of the benzene extract afforded a solid (260 mg., 65%), which was recrystallised from benzene. *1-Carbamoyl-3-phenyl-Δ²-pyrazoline* formed white crystals (Found: N, 21·4. $C_{10}H_{11}ON_3$ requires N, 22·2%), m. p. 157—160° not depressed by admixture with sample made as follows:

3-Dimethylamino-1-phenylpropan-2-one and hydrazine hydrate afforded 3-phenyl-Δ²-pyrazoline (Beech, Turnbull, and Wilson, *J.*, 1952, 4686), characterised by the nitroso-derivative, m. p. 154—156°. The pyrazoline (1·06 g.) was dissolved in 2N-hydrochloric acid (7·5 c.c.) at 40° (bath), and potassium cyanate (680 mg.) in water (2 c.c.) was added. The precipitated yellowish solid (440 mg.) was recrystallised from benzene, affording the carbamoyl compound, m. p. 157—160°.

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Complex-ion Formation. Part III. The Entropies of Reaction of the Silver and Hydrogen Ions with Some Aliphatic Amines.*

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The entropies of reaction of the methylamines and ethylamines with the silver ion and of the ethylamines with the hydrogen ion have been measured at 25° in aqueous solution. The different orders of base strength observed with the two acceptor ions find some explanation in the entropies of reaction.

WHEN the base strengths of amines are considered with reference to the silver and the hydrogen ion, although, in general, there is a close correlation between the orders, yet there are several exceptions. For instance, with reference to the hydrogen ion we have the orders of decreasing strength: $NHMe_2 > NH_2Me > NMe_3 > NH_3$; $NHEt_2 > NH_2Et > NEt_3 > NH_3$; while with the silver ion the order is $NH_3 > NH_2Me > NMe_3$; $NH_2Et > NH_3 > NHEt_2 > NEt_3$. It appears that steric effects may play an important part, indicated from the work of Brown and his co-workers (*J. Amer. Chem. Soc.*, 1945, **67**, 374, 378, 1452, 1767; 1948, **70**, 2802), and these effects should be demonstrated in the entropies of reaction.

Measurement of the entropy of reaction of ammonia with the silver ion has been described earlier (*J.*, 1952, 2023), and Everett and Wynne-Jones (*Trans. Faraday Soc.*, 1939, **35**, 1380) reported entropies of reaction of the hydrogen ion with ammonia and the methylamines.

In the present investigation the entropies of reaction of the ethylamines with the hydrogen ion have been obtained from measurements of the dissociation constants from 20° to 45°. The heats of reaction of the silver ion with methyl-, dimethyl-, ethyl-, and diethyl-amine were obtained by direct calorimetric measurement, and the free energies of formation of these complexes were obtained from simple concentration cells. In these cell measurements, the silver concentration was between 0·01 and 0·001M. In calculating the formation constants it was assumed that the activity coefficients were identical with those of silver nitrate at the same concentrations. Values of activity coefficients were taken from McInnes (*Chem. Reviews*, 1936, **18**, 341).

* Part II, *J.*, 1952, 2023.

Experimental

The heats of reaction of the methylamines and ethylamines with silver nitrate were measured in the calorimeters already described (*J.*, 1952, 2023). In all cases, 10 c.c. of M-silver nitrate were added to 100 c.c. of M-amine, and corrections for heats of dilution were made. The values of the heats of reaction are given in Table 5.

The free energies of formation of the silver complexes were obtained from silver-concentration cells with ammonium nitrate bridges. The constants obtained were, in comparable cases, in excellent agreement with those of Bjerrum (*Chem. Reviews*, 1950, **46**, 381). The entropies of reaction of the ethylamines with the hydroxonium ion were calculated from the temperature coefficients of the dissociation constants of the alkylammonium ions. Normally, in precise electrometric measurement of dissociation constants of acids and bases, a silver–silver chloride electrode is used with the hydrogen electrode to avoid junction potentials. However, the use of the silver chloride electrode is not desirable in cells containing a highly complexing amine, and the hydrogen electrode was used with a calomel electrode and a salt bridge. To attempt to minimise junction potentials Hitchcock and Taylor's method (*J. Amer. Chem. Soc.*, 1937, **59**, 1812) was used (see also Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, 1950). In this method the potential of the calomel electrode is redetermined so that it will give true dissociation constants at infinite dilution. In the present case the electrode was standardised by using the dissociation constant of ammonia determined by Everett and Wynne-Jones (*Proc. Roy. Soc.*, 1938, **169**, 190). A value of 0·2445 v was used for this potential with the normal temperature coefficients of the electrode (see Table 1).

All cells were of the type:

$$H_2(Pt) \mid \text{Amine, Amine } H^+ \mid \text{KCl satd.} \mid \text{KCl satd., } Hg_2Cl_2 \mid Hg$$

The hydrogen electrode was a platinum foil heavily coated with platinum black, and cylinder hydrogen was carefully purified by passing it over palladised copper in a tube furnace and saturated with water and amine at the same concentration as in the cell. All potentials were corrected to normal atmospheric pressure. Amines were purified by recrystallisation of the hydrochlorides, and solutions of the free amines were prepared by steam-distillation from alkali.

The following Tables summarise the results. The values for triethylamine are less accurate than those for other amines. With this amine, potentials tended to drift, and errors of 1—2 mv are possible. In the Tables, $E - E_0$ refers to the measured potential minus the standard calomel electrode potential; pK is the negative logarithm of the dissociation constant, and pK_0

Table 1. *Dissociation constant of the ammonium ion at* 25°: $E_0 = 0{\cdot}2445$ v.

$[NH_4^+] = 0{\cdot}0173$; $[NH_4OH] = 0{\cdot}0173$.

$E - E_0$	[KCl]	pK	$E - E_0$	[KCl]	pK	$E - E_0$	[KCl]	pK
0·5518	0·14	9·54	0·5468	0·06	9·39	0·5425	0·00	9·25
0·5485	0·10	9·45	0·5440	0·02	9·30		Mean pK_0	9·22

Table 2. *Dissociation constant of the ethylammonium ion.*

At 20°.

$E - E_0$	$[NH_3Et^+]$	$[NH_3Et]$	[KCl]	pK
0·6317	0·0349	0·0349	0·14	11·06
0·6317	—	—	0·10	11·00
0·6307	0·0241	0·0241	0·08	10·97
0·6280	—	—	0·04	10·90
0·6265	—	—	0·00	10·83
			Mean pK_0	10·79

At 25°.

$E - E_0$	$[NH_3Et^+]$	$[NH_3Et]$	[KCl]	pK
0·6349	0·0349	0·0349	0·14	10·95
0·6343	—	—	0·10	10·89
0·6319	0·0241	0·0241	0·08	10·85
0·6300	—	—	0·04	10·79
0·6291	—	—	0·00	10·71
			Mean pK_0	10·67

At 35°.

$E - E_0$	$[NH_3Et^+]$	$[NH_3Et]$	[KCl]	pK
0·6399	0·0349	0·0349	0·14	10·69
0·6384	—	—	0·10	10·64
0·6366	0·0241	0·0241	0·08	10·59
0·6353	—	—	0·04	10·50
0·6333	—	—	0·00	10·44
			Mean pK_0	10·40

At 45°.

$E - E_0$	$[NH_3Et^+]$	$[NH_3Et]$	[KCl]	pK
0·6347	0·0349	0·0349	0·14	10·42
0·6414	—	—	0·10	10·36
0·6409	0·0241	0·0241	0·08	10·33
0·6399	—	—	0·04	10·27
0·6377	—	—	0·00	10·18
			Mean pK_0	10·14

TABLE 3. *Dissociation constant of the diethylammonium ion:* $[NH_2Et_2^+] = 0.0192$; $[NHEt_2] = 0.0192$.

At 20°.			At 25°.			At 35°.			At 45°.		
$E - E_0$	[KCl]	pK	$E - E_0$	[KCl]	pK	$E - E_0$	[KCl]	pK	$E - E_0$	[KCl]	pK
0·6306	0·14	11·30	0·6491	0·14	11·18	0·6574	0·14	10·97	0·6494	0·14	10·70
0·6378	0·10	11·27	0·6488	0·10	11·15	0·6568	0·10	10·92	0·6486	0·10	10·66
0·6338	0·04	11·17	0·6475	0·04	11·08	0·6546	0·04	10·84	0·6469	0·04	10·58
0·6332	0·02	11·17	0·6458	0·02	11·03	0·6544	0·02	10·81	0·6468	0·02	10·55
0·6329	0·00	11·14	0·6466	0·00	11·02	0·6545	0·00	10·97	0·6470	0·00	10·53
Mean pK_0		11·11	Mean pK_0		10·98	Mean pK_0		10·76	Mean pK_0		10·50

is this value graphically extrapolated to zero ionic strength. Potassium chloride was added to most cells to vary the ionic strength.

DISCUSSION

Table 5 summarises the thermodynamic data calculated from the present results along with those of Everett and Wynne-Jones (*loc. cit.*). Free energies and heats are listed only to an accuracy consistent with experimental errors and are certainly no more accurate than this, as pK values are accurate to only ± 0·01. The entropies are probably only accurate to the nearest unit. In calculating the heats of reaction from the temperature coefficients it was assumed that log K is a linear function of $1/T$ and the data were fitted by least squares.

In Table 6 are summarised the formation constants of the various species determined in the present investigation along with those recently determined by other workers. It will be noticed that different workers seldom agree better than to approximately 0·1 in

TABLE 4. *Dissociation constant of the triethylammonium ion:* $[NHEt_3^+] = 0.0211$; $[NEt_3] = 00211$.

At 20°.			At 25°.			At 35°.			At 45°.		
$E - E_0$	[KCl]	pK	$E - E_0$	[KCl]	pK	$E - E_0$	[KCl]	pK	$E - E_0$	[KCl]	pK
0·619	0·14	11·03	0·634	0·14	10·93	0·641	0·14	10·70	0·634	0·14	10·46
0·619	0·10	10·99	0·634	0·10	10·89	0·640	0·10	10·65	0·634	0·10	10·42
0·615	0·06	10·90	0·629	0·06	10·78	0·637	0·06	10·58	0·630	0·06	10·33
0·614	0·02	10·84	0·630	0·02	10·76	0·637	0·02	10·53	0·630	0·02	10·29
0·615	0·01	10·83	0·629	0·01	10·72	0·635	0·01	10·49	0·628	0·01	10·24
Mean pK_0		10·78	Mean pK_0		10·67	Mean pK_0		10·45	Mean pK_0		10·21

TABLE 5. *Thermodynamic functions:* 25°.

A. Reaction: Amine + H^+ = Amine H^+.

Amine	$-\Delta G$ (kcal.)	$-\Delta H$ (kcal.)	ΔS (cal./mole)
NH_3 [a]	12·562	12·400	0·54
NH_2Me [a]	14·484	13·092	4·7
$NHMe_2$ [a]	14·721	11·880	9·5
NMe_3 [a]	13·384	8·828	15·3
NH_2Et	14·55	11·15	11·4
$NHEt_2$	14·97	10·3	15·7
NEt_3	14·55	9·7	16·3

B. Reaction: 2 Amine + Ag^+ = Ag Amine$_2^+$.

Amine	$-\Delta G$ (kcal.)	$-\Delta H$ (kcal.)	ΔS (cal./mole)
NH_3	9·85	13·5	−12·2
NH_2Me	9·26	11·5	− 7·5
$NHMe_2$	7·32	9·7	− 8·0
NH_2Et	9·98	13·0	−10·1
$NHEt_2$	8·70	10·65	− 6·5

[a] Everett and Wynne-Jones (*loc. cit.*).

TABLE 6.

	Temp.	Present result log K_H	Other workers log K_H		Temp.	Present result log K_{Ag}	Other workers log K_{Ag}
NH_2Et ...	18°	10·83	10·60 [a]	NH_3 ...	25°	7·22	7·23 [c]
	25	10·67	11·11,[b] 10·81 [c]	NH_2Me	25	6·79	6·68 [d]
$NHEt_2$ ...	18	11·18	11·16 [a]	$NHMe_2$	25	5·37	5·30 (18°) [a]
	25	10·98	11·11 [b]	NH_2Et...	25	7·32	7·30 (30°) [e]
	30	10·87	10·96 [f]	$NHEt_2$...	25	6·38	6·20 (30°) [f]
NEt_3 ...	18	10·83	10·81 [a]				
	25	10·67	10·80,[b] 10·77 [d]				

[a] Britton and Williams, *J.*, 1935, 796; 1936, 96. [b] Akerlof, *J. Amer. Chem. Soc.*, 1928, **50**, 733. [c] Bruehlman and Verhoek, *ibid.*, 1948, **70**, 1401 (0·5M-KNO_3). [d] Bjerrum, *Chem. Reviews*, 1950, *loc. cit.* (0·4M-amine nitrate). [e] Bjerrum, "Metal Ammine Formation" (corrected for salt). [f] Carlson, McReynolds, and Verhoek, *J. Amer. Chem. Soc.*, 1945, **67**, 1334 (0·5M-KNO_3).

pK. In the case of the amine ions the present method should be capable of better results than others as these are the only results calculated for zero ionic strength. In the case of the silver results the agreement between present results for ammonia corrected for activities and measured at low ionic strength and those of Bjerrum corrected for salt effects is very good. Other values are not immediately comparable owing to salt concentrations and the different temperatures used.

In all cases of proton amination the entropy of reaction is positive. Presumably, this effect is due to the smaller amount of hydration around the larger cations which will also be less polar. With increasing complexity of the amine the entropy of protonation becomes more positive, and this, in turn, should increase the stability of the ammonium ion. There are no obvious structural factors operating in these processes which account for the change in sign of the entropies of reaction in the two series. In general, we must suppose that the entropy of hydration of the hydroxonium ion is greater than that of the ammonium ion, while the same effect is not so pronounced when the silver aquo-cation is compared with the ammino-cation. This is not surprising, as the entropy of hydration is a function of size, and in the case of the small hydroxonium and ammonium ions, small differences will lead to large differences in entropy of hydration. With the larger complex ions of silver, small changes will have less effect, as these cations will have smaller entropies of hydration in the first place.

When the base strengths are considered, it is apparent from the data of Table 5 that in a series such as the methylamines, the heat-content term has the major effect in decreasing the strength of a base such as trimethylamine.

If the inductive effect was the most important influence trimethylamine should be the strongest base. The small value of ΔH for this base must arise very largely from repulsions introduced when rehybridisation necessary to form the more or less tetrahedral ammonium-type ion occurs. Rehybridisation must tend to crowd the methyl groups together. Such effects appear less pronounced when the chain lengthens in the ethylamines, for in such a group the polarity will be more widely spread. To some extent the same factors appear to influence combination with the silver ion but, as would be expected, the different size of the final grouping causes a different gradation in the position of appearance of such effects. It appears from the present results that perfect correlations between orders of base strength are not to be expected, as Brown *et al.* have already demonstrated so clearly.

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Absorption Spectra in Relation to the Chemical Reactivity of Some Halogeno-aromatic Compounds.

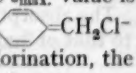
By F. SMITH and LILIAN M. TURTON.

[Reprint Order No. 5805.]

The ultra-violet light-absorption spectra of a number of chloro- and fluoro-aromatic compounds are described, and some correlation of the results with the degree of halogenation of the substances and their reactivity is attempted.

DURING studies on organic fluorides (*J.*, 1951, 1701 and others in the series), a number of chloro-aromatic compounds were obtained as intermediates (Harvey, Smith, Stacey, and Tatlow, *J. Appl. Chem.*, 1954, **4**, 319, 325). For many of these, no record of ultra-violet light absorption characteristics occurs in the literature and the relevant data are therefore tabulated below.

The spectra of *p*-xylene, benzene, benzyl fluoride, benzaldehyde, and benzoic acid have been compared by Ingold (*J.*, 1928, 2249), who observed a gradual displacement of wavelength of maximum absorption towards the blue which he correlated with the increasing

tendency of the substituent groups to deactivate the aromatic nucleus. Conrad-Billroth (*Z. physikal. Chem.*, 1932, **19**, *B*, 83) made a comprehensive survey of the spectroscopic properties of nuclear-substituted chlorobenzenes, and Sponer (*Chem. Reviews*, 1947, **41**, 281) has compared, in some detail, the absorption characteristics of 1 : 2 : 3-, 1 : 2 : 4-, and 1 : 3 : 5-trichlorobenzenes with those of the corresponding trimethylbenzenes. Hamner and Matsen (*J. Amer. Chem. Soc.*, 1948, **70**, 2482) point out the resemblance between the spectra of toluene and benzyl chloride. Benzylidene chloride exhibits a slight shift of maximum absorption towards the red and benzotrichloride behaves similarly, although the $\varepsilon_{max.}$ value is higher (300 and 500 respectively). These authors suggest forms such as  (I) to account for the results. The greater the degree of side-chain chlorination, the more of such forms can be postulated.

Our measurements and the data for the hydrocarbons, taken from Conrad-Billroth (*Z. physikal. Chem.*, 1935, **29**, *B*, 170), permit the comparisons in Table 1, where the numbers at the head of columns denote positions in the benzene ring :

TABLE 1.

	1	2	3	4	5	6	
i	Me	Me	—	—	—	—	λ 2700, 2640; ε 390, 415
	$CHCl_2$	CCl_3	—	—	—	—	λ 2790; ε 750
ii	Me	—	—	Me	—	—	λ 2740, 2680, 2650, 2600, 2555, 2510; ε 960, 726, 780, 545, 400, 330
	CH_2Cl	—	—	CH_2Cl	—	—	λ 2680; ε 300
	CCl_3	—	—	CCl_3	—	—	No selective absorption at λ 2700—2500, *i.e.*, low-wave-length absorption is so intense as to mask completely the " benzene " band
iii	Et	—	—	—	—	—	λ 2610; ε 220
	CCl_2·CCl_3	—	—	—	—	—	λ 2670, 2685; ε 800, 700
iv	Me	—	Me	—	Me	—	λ 2715, 2675, 2650, 2625, 2585, 2500; ε 266, 250, 303, 250, 273, 233
	CCl_3	Cl	CCl_3	—	CCl_3	—	No selective absorption at λ >2300

Some information about the effect of progressive halogen substitution in the side-chain of a nuclear chlorinated benzene derivative is afforded by the data in Table 2.

Except where the substituents are symmetrically placed (*e.g.*, the *p*-xylene and mesitylene derivatives with and without nuclear chlorine), these results support Hamner and Matsen's findings (*loc. cit.*) in that two or more side-chain chlorine atoms cause a considerable increase in the intensity of absorption. As is to be expected, the symmetrically substituted derivatives do not show the change, which is believed to be due to increase in the number of possible resonating forms.

TABLE 2.

	1	2	3	4	5	6	
i	Me	Cl	Cl	Cl	Cl	Cl	λ 2800; ε 240
	$CHCl_2$	Cl	Cl	Cl	Cl	Cl	λ 3070, 2920—3050; ε 885, 575
	CCl_3	Cl	Cl	Cl	Cl	—	λ 2920, 3000; ε 900 (approx.)
ii	Et	Cl	Cl	Cl	Cl	Cl	λ 2900; ε 195
	CH_2·CCl_3	Cl	Cl	Cl	Cl	Cl	λ 3070; ε 1170
	CCl_2·CCl_3	Cl	Cl	Cl	Cl	—	λ 3030, 2940; ε 1260, 1160
iii	Me	Me	Cl	Cl	Cl	Cl	λ 2800; ε 230
	$CHCl_2$	$CHCl_2$	Cl	Cl	Cl	Cl	λ 2900, 3105; ε 1060, 1280
iv	Me	Cl	Cl	Me	Cl	Cl	λ 2810; ε 260
	$CHCl_2$	Cl	Cl	$CHCl_2$	Cl	Cl	λ 3160; ε 2760
	CCl_3	Cl	Cl	CCl_3	Cl	Cl	λ 2900, 2930—3020; ε 300, 255
v	Me	Cl	Me	Cl	Me	Cl	λ 2780; ε 150
	$CHCl_2$	Cl	$CHCl_2$	Cl	$CHCl_2$	Cl	λ 2900 (" step out "); ε 400
	CCl_3	Cl	CCl_3	Cl	CCl_3	Cl	λ 2750—2850 (" step out "); ε 250 approx.

It was found that there is a relation between the type of spectrum a chloro-compound possesses and the ease with which the compound can be changed into the corresponding fluoro-compound by reaction with anhydrous hydrogen fluoride. When the spectrum of the chloro-compound resembles that of benzoic acid (λ 2270 Å, ε 14,000; with a shallow band at λ 2670 Å, ε *ca.* 1000; cf. Waljascko and Bottino, *Centralbl.*, 1915, **11**, 463), the conversion is relatively easy; if, however, the spectrum resembles that of the analogous

hydrocarbon or fluorocarbon, the reaction is difficult, if not impossible, as the following examples show:

(i) Anhydrous hydrogen fluoride cannot replace nuclear-substituted chlorine by fluorine, but trichloromethyl groups attached to nuclear carbon atoms are fluorinated easily. Fluorination of pentachloroethylbenzene in this way is difficult. It has been reported that the reaction $C_6H_5 \cdot CCl_2 \cdot CCl_3 \xrightarrow[HF]{\text{Anhyd.}} C_6H_5 \cdot CF_2 \cdot CCl_3$ occurs only at 200° and a hydrogen fluoride pressure of 3000 lb./sq. in., and Simons *et al.* (*J. Amer. Chem. Soc.*, 1921, **43**, 2064) record that vigorous fluorinating agents such as silver fluoride or antimony pentafluoride are necessary to introduce three or more fluorine atoms into its side-chain. The absorption spectrum of chlorobenzene closely resembles that of toluene and is similar to that of fluoro-

FIG. 1.

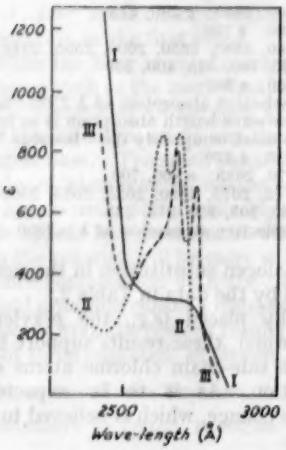


FIG. 2.

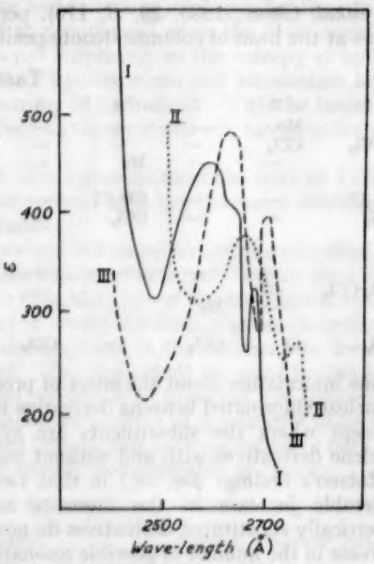


FIG. 1. *Absorption spectra of* (I) 1:4-*bischloromethylbenzene in* EtOH, (II) 1:4-*bistrifluoromethylbenzene in* cyclo*hexane, and* (III) *pentachloroethylbenzene in* cyclo*hexane.*

FIG. 2. *Absorption spectra of* (I) 1:1:1-*trichloro*-2:2-*diphenylethane*, (II) 1:1:1-*trichloro*-2:2-*di*-p-*chlorophenylethane, and* (III) 1:1:1-*trichloro*-2:2-*di*-p-*fluorophenylethane, all in* cyclo*hexane.*

benzene. Fig. 1 illustrates the similarity in spectrum type between 1:4-bistrifluoromethylbenzene and pentachloroethylbenzene. 1-Dichloromethyl-2-trichloromethylbenzene is likewise not easily fluorinated by anhydrous hydrogen fluoride and again its spectrum is of the toluene type. 1:4-Bischloromethylbenzene (Fig. 1) should be easily fluorinated by anhydrous hydrogen fluoride.

(ii) Dichlorodiphenylmethane readily reacts with anhydrous hydrogen fluoride to give difluorodiphenylmethane, although the difluoro-compound tends to be hydrolysed to benzophenone on being kept.

The difficulty of the replacement of chlorine by fluorine follows approximately the same order as the amount of *meta*-direction of a nitro-group entering the ring (caused by the chlorine-containing substituent) (cf. Rice, "The Mechanism of Organic Reactions," McGraw-Hill, New York, p. 146; Hamner and Matsen, *loc. cit.*; Flürscheim and Holmes, *J.*, 1928, 1607).

It is well known that the halogens are capable not only of attracting electrons but also of donating them in suitable circumstances, *e.g.*, the relative strengths of the acids

$F{\cdot}CH_2{\cdot}CO_2H$, $Cl{\cdot}CH_2{\cdot}CO_2H$, $CH_3{\cdot}CO_2H$ decrease in the order given (inductive attraction of electrons by F > Cl > H), whereas a nuclear halogen atom is largely *ortho-para*-directing to an incoming electrophilic substituent (activation of *ortho*- and *para*-positions by the electromeric donor effects of halogens). The groups CH_2F and CH_2Cl are also largely *ortho-para*-directing, the inductive attraction of electrons not becoming marked until two side-chain halogen atoms are present. It should be noted that the resonance forms

TABLE 3.

Compound	Yield of mononitro-compound (%) *o*-	*m*-	*p*-
Chlorobenzene	30·1	—	69·9
Toluene	61·5—62·5	4·5—4·2	33·5—32
Benzyl chloride	40·9	4·2 *	54·9
Benzylidene chloride	23·3	33·8	42·9
Benzotrichloride	6·8	64·5 *	28·7
Benzoic acid	18·5	80·2	1·3

* Flürscheim and Holmes, *loc. cit.*, give 11·2 and 48·3—48·6%, respectively.

postulated by Hamner and Matsen would deactivate the *ortho*- and *para*-positions [see (I)]. The following experimental results suggest that successive nuclear chlorination makes the electromeric effect subsidiary to the inductive effect: (i) One chlorine atom in hexachlorobenzene is quite easily hydrolysed. (ii) The chlorine in *m*-dichlorobenzene is more reactive towards sodium methoxide than in the *o*- and *p*-isomers. (iii) The nuclear chlorine atoms in 1 : 3 : 5-trichlorobenzene are relatively reactive and resemble to some extent that in picryl chloride. In this, the three attractor groups present cause the nuclear chlorine to be labile as in an acid chloride group.

In this connection, Fig. 2 is of interest. The fluoro-substituted compound has a band of slightly higher intensity than the unsubstituted molecule; the chloro-substituted compound is of very slightly lower intensity; the orders of magnitude, however, are the same in each case. The shift towards the red is greatest in the case of the nuclear chloro-substituted derivative. The relative intensities are such as to suggest that fluorine is a better donor than chlorine, which is in agreement with the finding by Kharasch *et al.* (*J. Org. Chem.*, 1938, **3**, 347) that the ease of cleavage in the reaction $R{\cdot}Hg{\cdot}R' + HCl \longrightarrow R{\cdot}Hg{\cdot}Cl + R'H$ (R′ is the more electronegative) decreases in the order *p*-fluorophenyl > phenyl > *p*-chlorophenyl.

A correlation of the directive effects of a number of groups on substituents entering a benzene ring to which they are attached with their dipole moments in aromatic (ar) and aliphatic (al) combination, made by Sutton (*Proc. Roy. Soc.*, 1931, **133**, 686), affords a preliminary unification of these various data. He showed that when $\mu_{al} > \mu_{ar}$ the group deactivates the nucleus and is *meta*-directing. Some values of the difference $(\mu_{ar} - \mu_{al})$ are given in Table 4.

TABLE 4. *Dipole moments of some organic groups.*

(Unless stated otherwise the following data are due to Sutton, *loc. cit.*)

Group	μ_{ar}	μ_{al}	Diff.	Group	μ_{ar}	μ_{al}	Diff.
Cl	−1·56	−2·15	+0·59	CCl_3	−2·07	−1·57	−0·50
F [1]	−1·57	−1·92	+0·35 [1]	CH_3	+0·45	0·0	+0·45
CH_2Cl	−1·82	−2·03	+0·21	CO_2Et	−1·95	−1·77	−0·18
$CHCl_2$	−2·03	−2·06	+0·03	CO_2H [2]	−0·56	—	—

[1] Groves and Sugden, *J.*, 1935, 972. [2] Conrad-Billroth, *Z. physikal. Chem.*, 1934, **25**, *B*, 139.

Both CCl_3 and CO_2Et deactivate the benzene nucleus, and it was noted above that the spectra of benzotrichloride and of ethyl benzoate are similar. It will be seen that μ_{al} is more negative for CO_2Et than for CCl_3, while μ_{ar} is approximately the same. Trichloromethyl groups directly attached to the benzene nucleus are readily fluorinated, whereas the CCl_3 group in ethyl trichloroacetate does not react with anhydrous hydrogen fluoride under the same conditions (Amphlett, Musgrave, and Smith, unpublished results). This would follow if the reaction depended on electrons' being drawn into the CCl_3 group from

the rest of the molecule. If the spectrum type is governed by the same consideration, then the values of dipole moments of the CF_3 group in aliphatic and aromatic combination will prove of interest, in that μ_{ar} and μ_{al} for this group should both be smaller than the corresponding values for CCl_3. ($\mu_{ar} - \mu_{al}$) must be negative to fall into line with the known *meta*-directing properties, while to account for the difference in spectrum between CF_3 and corresponding CCl_3 derivative, μ_{ar} must have a smaller negative value for the fluoro- than for the chloro-compound. This would be expected if resonance forms of the type $-\overset{+}{C}\!<\!\begin{matrix}F\\F\end{matrix}$ F^- are prominent (see Smith and Turton, *J.*, 1951, 1701). All the available information appears to support this view.

Experimental.—The spectrophotometric measurements were carried out as described by Smith and Turton (*loc. cit.*).

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The University of Birmingham. [*Received, October 15th*, 1954.]

Tracer Studies on Ester Hydrolysis. Part I. Triphenylmethyl Acetate.

By C. A. Bunton and (Mrs.) Alicja Konasiewicz.

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The kinetics of hydrolysis and methanolysis of triphenylmethyl acetate have been examined in aqueous dioxan and absolute methyl alcohol respectively. The position of bond fission has been determined by the use of ^{18}O as a tracer in hydrolysis, and by product-isolation in methanolysis. The results show that in initially neutral and weakly alkaline solutions the reactions follow the mechanism $B_{Al}1$. Both reactions are subject to powerful acid-catalysis, with predominant fission of the alkyl–oxygen bond, by mechanism $A_{Al}1$. With an increase in alkali concentration the mechanism $B_{Ac}2$ intervenes. The effects of added ions have been studied, and can be interpreted in terms of a rate-determining formation of a carbonium ion in the reactions which involve fission of the alkyl–oxygen bond.

The hydrolysis of carboxylic esters, in the presence of acids and bases, and the analogous transesterification reactions with alcohols, normally proceed with fission of the acyl–oxygen bond. Day and Ingold (*Trans. Faraday Soc.*, 1941, **37**, 686), however, pointed out that fission of the alkyl–oxygen bond would be facilitated by electron accession to the α-alkyl-carbon atom. Such systems are those in which the lability of the alkyl–oxygen bond in esters, alcohols, and ethers has been demonstrated by racemisation (Kenyon and his co-workers, papers beginning in *J.*, 1937), and other examples include the ethanolysis of triphenylmethyl benzoate (Hammond and Rudesill, *J. Amer. Chem. Soc.*, 1950, **72**, 2769), and the methanolysis and hydrolysis of *tert.*-alkyl esters (Cohen and Schneider, *J. Amer. Chem. Soc.*, 1941, **63**, 3382; Bunton, Comyns, and Wood, *Research*, 1951, **4**, 383; Bunton, Hughes, Ingold, and Meigh, *Nature*, 1950, **166**, 679).

The position of bond fission in alcoholysis is proved directly by the nature of the products:

(*a*) $CH_3{\cdot}CO|{-}O{\cdot}CPh_3 + ROH \rightleftharpoons CH_3{\cdot}CO_2R + CPh_3{\cdot}OH$

(*b*) $CH_3{\cdot}CO{\cdot}O{-}|CPh_3 + ROH \longrightarrow CH_3{\cdot}CO_2H + CPh_3{\cdot}OR$

In hydrolysis the position of bond fission can often be determined by means of some property dependent on the type of alkyl group (Kenyon and his co-workers, *locc. cit.*), but a more general method is that using ^{18}O as isotopic tracer (Polanyi and Szabo, *Trans. Faraday Soc.*, 1934, **30**, 508).

Product formation in alcoholysis as a criterion of bond fission lacks the sensitivity of the isotopic tracer method, and moreover may give misleading results unless kinetic control is applied. Transesterification [reaction (*a*)] is reversible, whereas ether formation [reaction

(*b*)], is irreversible, and thermodynamic control may therefore force the products into those of reaction (*b*) independently of mechanism (cf. Bunnett, Robison, and Pennington, *J. Amer. Chem. Soc.*, **1950**, **72**, 2328, who with methyl benzoate with sodium methoxide in methanol, where transesterification regenerated the reactants, were able to observe the very slow attack of the methoxide ion on the alkyl-carbon atom).

Hydrolysis in Aqueous Dioxan.—Fission of the alkyl–oxygen bond, which is of major importance in alcoholysis of triphenylmethyl acetate, is also observed in hydrolyses carried out in various conditions in aqueous dioxan. The reactions were carried out with water enriched in ^{18}O, and the position of bond fission given directly by isotopic analysis of the products, since alkyl–oxygen fission (*b*) gives ^{18}O only in the alcohol, and acyl–oxygen fission gives it only in the acid. Isotopic oxygen exchange between water and the ester, shown by Bender (*J. Amer. Chem. Soc.*, **1951**, **73**, 1626) to occur with acyl–oxygen fission, does not interfere since all our reactions involve predominantly alkyl–oxygen fission.

In general, the position of bond fission was determined by isolation of the acetic acid as its silver salt, and isotopic assay of the carbon dioxide produced by decarboxylation of this salt. As a supplement, triphenylmethyl alcohol was on occasions isolated and pyrolysed to carbon monoxide whose isotopic abundance (α) was determined by mass spectrometry. Blank tests excluded extraneous isotopic exchange by the products. The results (Tables 1 and 2) show that in all conditions alkyl–oxygen fission predominates, although in alkaline solution there is a small amount of acyl–oxygen fission. It is probable that the mechanism could be forced into that of acyl–oxygen ($B_{Ac}2$), by a large increase in alkali concentration if this were not precluded by the low solubilities of the ester and the alkali in aqueous dioxan (although the analogous product can be isolated in methanolysis); even in some of the hydrolyses with our low concentrations of alkali, slight cloudiness indicated separation into two phases. Such experiments are marked ‡ in Table 1.

TABLE 1. *Position of bond fission in hydrolysis in 80% dioxan, determined by isolation of acetic acid.*

Conditions	α for H_2O (atoms % excess)	α for $CH_3{\cdot}CO_2H$ (atoms % excess)	Alkyl–oxygen fission (%) *
Initially neutral	1·134	0·03, 0·04	96, 94
Alkaline, 0·015M-NaOH †	,,	0·127, ‡ 0·127 ‡	78, 78
0·028M-LiOH	0·846, 1·07	0·063, 0·098	85, 82
Acid, 0·0446M-$HClO_4$	1·134	0·058	94
0·037M-$HClO_4$	1·93	0·116	92

In control tests (α_{H_2O} 1·134), $\alpha_{CH_3{\cdot}CO_2H}$ was 0·003—0·007, 0·00—0·002, and 0·024 (twice) for initially neutral, alkaline, and acid (0·0446M-$HClO_4$) respectively.

* Corrected for controls. † In aqueous 71·5% dioxan. ‡ See text.

TABLE 2. *Position of bond fission in hydrolysis, determined by isolation of triphenylmethyl alcohol.*

Conditions	α for H_2O (atoms % excess)	α for $Ph_3C{\cdot}OH$ * (atoms % excess)
Acid, 0·03701M-$HClO_4$	1·93	1·84
0·036M-$HClO_4$	0·442	0·410, 0·420
Initially neutral	0·442	0·398, 0·407
Controls.		
Acid, 0·036M-$HClO_4$	0·442	0·094
Initially neutral	0·442	0·060

* Corrected for contamination of ester by alcohol (2—3%).

The kinetics of hydrolysis were followed titrimetrically, for initially neutral conditions, in the presence of acids and bases and with added salts (see Table 3). The effects of alkali and neutral salts are not large, but there is very marked acid-catalysis, the rate with M-sulphuric acid being *ca.* 3000 times that under initially neutral conditions. This general kinetic form is very similar to that observed in methanolysis. The isotopic results on bond fission show that both these reactions involve alkyl–oxygen fission, and the neutral

reaction, proceeding at similar rates in neutral and alkaline solutions, can be only the rate-determining ionisation of the ester molecule; it is followed by rapid reaction between the triphenylmethyl cation and the aqueous solvent (the mechanism $B_{Al}1$ of Day and Ingold, *loc. cit.*):

$$\left.\begin{array}{l} CH_3{\cdot}CO{\cdot}O{-}|CPh_3 \overset{\text{Slow}}{\rightleftharpoons} CH_3{\cdot}CO{\cdot}O^- + CPh_3^+ \\ Ph_3C^+ + H_2O \xrightarrow{\text{Fast}} CPh_3{\cdot}OH + H^+ \end{array}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (A)$$

Analogously the acid-catalysed mechanism must involve the ionisation of the conjugate acid of the ester (mechanism $A_{Al}1$):

$$CH_3{\cdot}CO_2CPh_3 + H^+ \overset{\text{Fast}}{\rightleftharpoons} [CH_3{\cdot}CO_2H{\cdot}CPh_3]^+$$

$$[CH_3{\cdot}CO_2H{\cdot}CPh_3]^+ \overset{\text{Slow}}{\rightleftharpoons} CH_3{\cdot}CO_2H + CPh_3^+$$

$$Ph_3C^+ + H_2O \xrightarrow{\text{Fast}} CPh_3{\cdot}OH + H^+$$

The isotopic results in alkaline solution indicate the presence of a small amount of acyl–oxygen fission. This mechanism ($B_{Ac}2$) is dependent on hydroxide-ion concentration:

$$CH_3{\cdot}CO{|}{-}O{\cdot}CPh_3 + OH^- \longrightarrow CH_3{\cdot}CO_2^- + CPh_3{\cdot}OH$$

It should lead to a corresponding increase of rate by hydroxide ion, which however is not observed (although the results in alkaline solution are much more scattered than in initially neutral solution). Various reasons are possible for this: (i) Benfey, Hughes, and Ingold,

TABLE 3.

Solvent (% of dioxan)	Temp.	Reagent or catalyst	Concn. of reagent (moles l.$^{-1}$)	10^4k_1 (sec.$^{-1}$)	Solvent (% of dioxan)	Temp.	Reagent or catalyst	Concn. of reagent (moles l.$^{-1}$)	10^4k_1 (sec.$^{-1}$)
80	65·0°	—	—	8·31 [a]	82·5	65·0°	—	—	4·00
,,	,,	AcOH	0·03	8·50	85·0	,,	—	—	1·46
,,	,,	$Et_4N{\cdot}OH$	0·0263	6·64	80	35·1	—	—	0·253
,,	,,	,,	,,	7·22	,,	44·6	—	—	0·86 [b]
,,	,,	Et_3N	0·00031	7·20	,,	55·2	—	—	2·72 [b]
,,	,,	C_5H_5N	0·00025	7·52	,,	25·0	H_2SO_4	0·0116	2·14
,,	,,	,,	0·0025	7·67	,,	,,	,,	0·0229	5·25
,,	,,	LiOH	0·0297	7·67	,,	,,	,,	0·0233	5·75
,,	,,	,,	0·0266	7·50 [b]	,,	,,	,,	0·0349	7·45
,,	,,	LiCl	0·294	6·14	,,	,,	,,	0·0418	9·59
,,	,,	LiOAc	0·272	1·92	85	,,	,,	0·0229	4·05
81	,,	—	—	5·75	90	,,	,,	0·0229	3·40

[a] Mean of 5 values. [b] Mean of 2 values.

(*J.*, 1952, 2494) have shown that hydroxide ions can have a weak retarding effect on S_N1 reactions in aqueous solvents. (ii) As would be predicted, the rate of hydrolysis is highly dependent on the water content of the solvent, a decrease of the water content by 5 vol. % giving *ca.* sixfold decrease in rate (Table 3), and co-ordination of water with the lithium cation could reduce the rate by reducing the effective water content of the solvent (Lucas and Hammett, *J. Amer. Chem. Soc.*, 1942, **64**, 1928).

It is possible that this " salting-out " effect of a metal cation is also responsible for the decrease of hydrolysis rate in the presence of the non-common-ion salt lithium chloride (Table 3), whereas such salts usually accelerate S_N1 reactions (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979). It is noteworthy that lithium acetate, which should give a " mass-law " retardation of the S_N1 reaction of this ester, in fact shows a considerably greater retardation than does lithium chloride (Table 3). It seems therefore that salt-effects on the ionisation of the neutral ester molecule are complicated by solvation of the lithium cation. This complication is absent from reactions in methyl alcohol which provides a more convenient solvent for kinetic study of the effects of alkali ions and of neutral salts.

Tetraethylammonium hydroxide slightly retarded hydrolysis: it seemed possible that this was due to small amounts of triethylamine initially present or formed during the

reaction. Indeed, small amounts of tertiary bases also retarded the hydrolysis, presumably by co-ordination with the carbonium ion, thereby delaying its capture by the water molecules (cf. Gelles, Hughes, and Ingold, *J.*, 1954, 2918).

The corresponding solvent effect on the acid-catalysed hydrolysis rate is somewhat more complicated. Experimentally we observe a small rate increase (*ca.* 40%) in going from aqueous 90% dioxan to the more aqueous solvent, aqueous 80% dioxan. Theoretically one expects a two-fold effect, on the protonation of the neutral molecule and on the breakdown of the protonated molecule. Indicator measurements with hydrochloric acid in aqueous dioxan (Braude and Stern, *J.*, 1948, 1976) show that in the solvent range used in our hydrolyses the tendency to donate a proton to a neutral base decreases with an increase in the water content of the solvent. If this is also true of sulphuric acid the breakdown of the protonated ester molecule must be facilitated by an increase in the water content of the solvent. By analogy with the S_N1 reactions of sulphonium salts we would expect a retardation of breakdown of the protonated ester molecule, but it is probable that the presence of the polar carbonyl group complicates this simple analogy.

The temperature coefficient of the neutral hydrolysis was measured in aqueous 80% dioxan to allow a comparison to be made between the neutral and the acid rate. The "activation energy," in the exponential term in the Arrhenius equation, was 23·6 kcal./mole, and that for the non-exponential term was $2{\cdot}6 \times 10^{12}$ sec.$^{-1}$.

Reactions in Absolute Methyl Alcohol.—Neutral and alkaline solution. Gomberg and Davies (*Ber.*, 1903, **36**, 3926) observed that triphenylmethyl acetate and benzoate in ethyl alcohol gave ethyl triphenylmethyl ether, and similarly we observe the formation of methyl triphenylmethyl ether in methyl alcohol both initially neutral and in the presence of 0·1M-sodium methoxide. Control tests showed that this product could not have been formed by a side reaction between triphenylmethyl alcohol and methyl alcohol.

The rates of methanolysis were measured by acid–alkali titration, in initially neutral solution and with sodium methoxide. The kinetic form was generally similar to that observed in the reaction of triphenylmethyl benzoate in an ethyl alcohol–ethyl methyl ketone solvent (Hammond and Rudesill, *loc. cit.*). The reaction observed is a neutral solvolysis, whose rate is independent of acid and base (Table 4), and the kinetic form and product isolation prove that it must be following the mechanism $B_{Al}1$ (cf. reactions *A*, p. 1356). The effects of added lithium acetate and chloride are in accord with this mechanism, the former showing a mass-law retardation typical of an S_N1 reaction, and the latter a typical ionic-strength acceleration.

TABLE 4.

Temp.	Reagent or catalyst	Concn. of reagent (mole/l.$^{-1}$)	10^4k_1 (sec.$^{-1}$)	Temp.	Reagent or catalyst	Concn. of reagent (mole/l.$^{-1}$)	10^4k_1 (sec.$^{-1}$)
35·1°	—	—	9·94 [a]	20·0°	—	—	1·77
,,	NaOMe	0·066	9·73	,,	NaOMe	0·324, 0·869	3·11,[c] 5·20[c]
,,	,,	0·112	9·87	35·1	LiCl	0·076	11·08
	Mean in presence of NaOMe		9·80 [b]	,,	LiOAc	0·076	8·98

[a] Mean of 4 values. [b] Mean of 5 values. [c] Detd. by dilatometry.

With higher concentrations of sodium methoxide (*ca.* 1·6M) triphenylmethyl alcohol was isolated from the reaction mixture, suggesting the intervention of the base-accelerated mechanism ($B_{Ac}2$) :

$$CH_3{\cdot}CO{-}OCPh_3 + OMe^- \rightleftharpoons CH_3{\cdot}CO_2Me + CPh_3{\cdot}O^-$$

$$CPh_3{\cdot}O^- + MeOH \rightleftharpoons CPh_3{\cdot}OH + MeO^-$$

This formally reversible reaction is driven to the right-hand side because the second equilibrium is heavily in favour of the methoxide ion and the triphenylmethyl alcohol in our experimental conditions. The total concentration of alkoxide ion does not change during the reaction, and it is therefore impossible to follow this reaction by direct acid–alkali titration, but it can be followed dilatometrically. This method is not entirely satisfactory, the volume changes being small, and, if the fission is not purely of the acyl–oxygen bond, a change in alkoxide-ion concentration occurs during the run and the

order should deviate from unity. The limited results obtained (Table 4), show a definite acceleration of transesterification by a high concentration of methoxide ion and, with the product isolation, demonstrates the existence of the $B_{Ac}2$ mechanism in this system.

With intermediate concentration of methoxide ion (*ca.* 0·3M) the two mechanisms should co-exist, with a mixture of acyl–oxygen and alkyl–oxygen fission. Both are of the first order with respect to ester, but in the acyl–oxygen fission of first order with respect to the approximately constant concentration of methoxide ion. It should therefore be possible to predict approximately the product compositions from the measured rates. The proportions of the two mechanisms were estimated by measurement of the triphenylmethyl ether (giving the proportion of alkyl–oxygen fission) and of methyl acetate (giving that of acyl–oxygen fission). The results obtained with 0·324M-sodium methoxide at 20° are given in the Experimental section; they are probably as good as can be expected from a method which is sensitive to the fractionation errors of product isolation. Comparison of the observed and the calculated product proportions suggests that the assumptions involved in the use of dilatometry for the measurement of reaction rates at these high alkali concentrations are justified.

Acid solution. In the presence of even small concentrations of dry hydrogen chloride (*ca.* M/30) the methanolysis becomes too fast for convenient measurement. Under these conditions methyl triphenylmethyl ether was again isolated, but under comparable conditions a control test showed that the alcohol in methanol gave 27% of this ether and it is therefore impossible to exclude completely the existence of the acid-catalysed acyl–oxygen fission ($A_{Ac}2$); but, if this mechanism obtains, it is of minor importance compared with the mechanism $A_{Al}1$.

The Arrenhius parameters for neutral methanolysis (deduced from two temperatures only) are, for the "activation energy" 20·5 kcal./mole, and for the non-exponential term $4{\cdot}0 \times 10^{11}$ sec.$^{-1}$.

Experimental

Preparation of Materials.—Methyl alcohol was dried over magnesium by Lund and Bjerrum's method (*Ber.*, 1931, **64**, 210) and further purified by fractional distillation.

Dioxan was purified by refluxing it with dilute hydrochloric acid in a stream of nitrogen, drying it first over potassium hydroxide, then over metallic sodium, and finally distilling it from sodium.

Solutions of aqueous dioxan were made up by volume, *e.g.*, aqueous 80% dioxan by mixing 20 vols. of water with 80 vols. of dioxan at room temperature.

Sodium methoxide solutions were prepared by dissolving sodium, freshly washed in dry methyl alcohol, in dry methyl alcohol.

Triphenylmethyl acetate was prepared by the general methods of Gomberg and Davies (*loc. cit.*). Excess of dried silver acetate was refluxed with triphenylmethyl chloride in dry benzene for 3 hr., or, better, shaken with triphenylmethyl chloride in dry ether until reaction was complete (*ca.* 48 hr.). After filtration and evaporation of the solvent the crude ester was purified by recrystallisation from light petroleum, light petroleum–ethyl acetate, or preferably di*iso*propyl ether. The ester decomposed when kept in a desiccator, and freshly prepared samples were used. A typical specimen had m. p. 83° (Found: C, 83·6; H, 5·9. Calc. for $C_{21}H_{18}O_2$: C, 83·4; H, 6·0%).

Tetraethylammonium hydroxide solutions were prepared by refluxing tetraethylammonium iodide with ethyl iodide, washing the mixture with ether to remove unchanged ethyl iodide and any triethylamine, and shaking the tetraethylammonium iodide solution with excess of silver oxide in carbonate-free water.

Lithium hydroxide was prepared similarly by treating lithium chloride with silver oxide in carbonate-free water.

Reactions in Aqueous Dioxan.—Position of bond fission. Hydrolysis of the ester was carried out in aqueous dioxan under kinetic conditions, with water enriched in ^{18}O. After reaction the solvent was removed under reduced pressure, the residue neutralised, and the acetic acid isolated as silver acetate. After drying, first over P_2O_5, and then in a high vacuum, the silver acetate was decarboxylated by heating *in vacuo*. The carbon dioxide was analysed for ^{18}O in a 180° mass spectrometer of conventional design.

When the triphenylmethyl alcohol was isolated it was purified by crystallisation from light

petroleum, and its isotopic abundance determined by pyrolysis *in vacuo* in a carbon tube heated by a 1-kw R.F. induction heater. The carbon monoxide was collected over liquid air and analysed mass-spectrometrically. This general method has been checked by catalytic conversion of the carbon monoxide into carbon dioxide, and the absence of air-contamination was shown by the absence of argon. The isotopic abundances (α) quoted are in atoms % of ^{18}O above normal, determined for the acid and alcohol by the above methods, and for the water by equilibriation with carbon dioxide.

If R is the ratio of the peaks, for $^{12}C^{16}O^{16}O$ and $^{12}C^{16}O^{18}O$, and for $^{12}C^{16}O$ and $^{12}C^{18}O$, then the abundances of ^{18}O are given in atoms % by :

for CO_2, $\alpha' = 100/(2R + 1)$;

for H_2O, $\alpha' = 100/(2KR + 1)$, where $K = 1{\cdot}038$ at 25°;

for CO, $\alpha' = 100/(R + 1)$

and the excess abundance, $\alpha = \alpha'$(sample) $- \alpha'$(normal).

Control experiments were carried out by the same methods and under the same conditions.

Kinetics. The reactions were followed by acid–alkali titration with thymol-blue as indicator. Those catalysed by sulphuric acid at 25° were carried out in stoppered flasks, but sealed tubes were used at higher temperatures.

Reactions in Absolute Methyl Alcohol.—The products of methanolysis were isolated in good yield from kinetically controlled reactions; *e.g.*, in initially neutral methyl alcohol at 35° the ester (6 g.) after 5 hr. gave the methyl triphenylmethyl ether, m. p. 83·5°, in 82% yield.

Similarly the ester (0·85 g.) with 1·7M-sodium methoxide gave after 4 hr. at 35° triphenylmethyl alcohol, m. p. 162°, in 55% yield.

In an experiment with 0·324M-sodium methoxide 0·293 g. of ester gave after 4 hr. at 20° 63·6% of methyl triphenyl ether (estimated by methoxyl determination on the solid residue), and 34% of methyl acetate (estimated by alkaline hydrolysis of the distillate). This gives a proportion of alkyl–oxygen fission of *ca.* 64% (the value estimated from the kinetics is 57%).

The products obtained are listed in Table 5. Control tests showed that the alcohol was not converted into the ether under neutral or alkaline conditions.

TABLE 5. *Products of methanolysis.*

Reagent	Product	Yield (%)	Fission	Reagent	Product	Yield (%)	Fission
Neutral	Ether	82	Alkyl	0·1N-NaOMe	Ether	83	Alkyl
M/30-HCl	Ether	75	Alkyl	1·7M-NaOMe	Alcohol	55	Acyl
M/30-HCl (control)	Ether (27%) *	—	—	0·33M-NaOMe ...	Alcohol	34 †	Mixed
					Ether	64	

* Estimated from OMe determination of solid product. † Estimated indirectly.

Kinetics. The reaction was followed by acid–alkali titration, where possible, with thymol-blue–cresol-red as indicator. In concentrated alkali the reaction proceeded without change of alkalinity, and the reactions were therefore followed by dilatometry. Dilatometers of the tap-less two-arm type were used (Benford and Ingold, *J.*, 1938, 931), the movement of the meniscus being followed by a cathetometer, and the thermostat temperature controlled to *ca.* 0·001°. First-order rate coefficients were obtained graphically by Guggenheim's method (*Phil. Mag.*, 1926, **2**, 538). A typical result is tabulated.

Temp. 20·0°. $[Ester]_0 = 0{\cdot}0406$M. Portions of 5·00 c.c. titrated against 0·0413M-NaOH; $(a - s)$ expressed in c.c. of this NaOH. A mixed indicator of thymol-blue and cresol-red was used.

t (min.)	0	13·0	16·0	19·0	25·5	33·0	44·0	52·5	60·0	70·33	80·33	120
$(a - x)$	4·92	4·28	4·18	4·00	3·80	3·47	3·05	2·83	2·59	2·34	2·03	1·31
10^4k_1 (sec.$^{-1}$) ...	—	1·80	1·72	1·81	1·66	1·77	1·75	1·75	1·78	1·77	1·78	1·72

Mean value of $10^4k_1 = 1{\cdot}77$ sec.$^{-1}$.

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Reactions of Unsaturated Compounds. Part XII. The Course of Oxidation of Olefins by Chromic Acid.*

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The results of oxidation of some olefins by chromic acid in aqueous sulphuric acid and by chromic oxide in acetic anhydride, are compared, and a hypothesis to account for them is developed.

Two epoxides have been oxidised to 1 : 2-diketones.

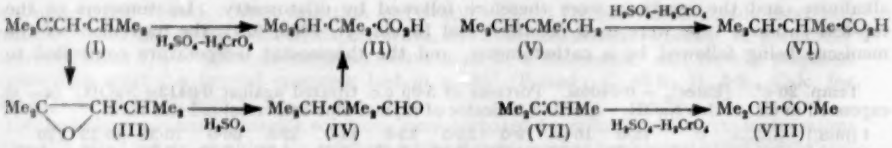
Oxidation of 2 : 4-dimethylpent-2-ene (I) by chromic oxide in acetic anhydride diluted with carbon disulphide gives the corresponding epoxide (III) with no important quantity of other products. Other olefins examined in this work give lower yields and the products contain appreciable amounts of αβ-unsaturated ketones as well as substances derived from oxidative fission of the double bond. The products isolated from each olefin are given in the accompanying Table, the yield of epoxide descending in the order given.

It appears from these and earlier results (*J.*, **1948**, 1334; **1951**, 1600; **1953**, 1906; **1954**, 4400) that the yield of epoxide on oxidation by chromic oxide is greatest when one of the unsaturated carbon atoms of the olefin carries no hydrogen atom Thus *cyclo*hexene gave only a poor yield of epoxide and none could be isolated from pent-2-ene or oct-1-ene

Olefin	Products of oxidation
2 : 4-Dimethylpent-2-ene	Epoxide
2-Methylbut-2-ene	Epoxide, 3-methylbutan-2-one, 3-methylbut-2-enal, 3-methylbut-3-en-2-one
2 : 3-Dimethylbut-1-ene	Epoxide, 3-methylbutan-2-one, 2 : 3-dimethylbut-2-enal
*cyclo*Hexene	*cyclo*Hex-2-enone, epoxide, *cyclo*hexane-1 : 2-dione
Pent-2-ene	Pent-3-en-2-one, pentane-2 : 3-dione
Oct-1-ene	Hexanoic and heptanoic acid, oct-1-en-3-one (in acetic acid : 1-acetoxyoctan-2-one)

although the formation of an epoxide from oct-1-ene may be reasonably inferred from the formation of 1-acetoxyoctan-2-one when the oxidation is carried out in acetic acid. The low yield from these olefins may be due to competition with other reactions or to the instability of the epoxide in the oxidising solution. It is shown (p. 1364) that the αβ-diketones which are products of the oxidation of pent-2-ene and of *cyclo*hexene can arise by further oxidation of the epoxide.

It was established earlier (*J.*, **1954**, 4400) that oxidation of 2 : 3-dimethylbut-2-ene by chromic acid in aqueous sulphuric acid of more than 50% concentration gave appreciable amounts of 3 : 3-dimethylbutan-2-one. Under similar conditions, 2 : 4-dimethylpent-2-ene



(I) gives ααβ-trimethylbutyric acid (II) together with the normal products of oxidative fission, acetone and *iso*butyric acid. The acid (II) can be formed by oxidation of the rearrangement product in sulphuric acid of the glycol or of the epoxide (III).

The formation of 2 : 3-dimethylbutanoic acid (VI) from 2 : 3-dimethylbut-1-ene (V) and of 3-methylbutan-2-one (VIII) from 2-methylbut-2-ene (VII) can be accounted for similarly. Indeed all the recorded examples of the oxidation of an olefin by sulphuric–chromic acid to a product with the same number of carbon atoms (Butleroff, *Annalen*, **1877**, **189**, 44; Whitmore and Surmatis, *J. Amer. Chem. Soc.*, **1941**, **63**, 2200; Hickinbottom *et al.*, *locc. cit.*) find a simple explanation in terms of the intermediate formation

* Part XI, *J.*, **1954**, 4400.

of an epoxide or glycol. The assumption that a glycol is an intermediate is unlikely since no rearrangement products have been detected when glycols are treated with chromic acid in 55—60% sulphuric acid. Indeed oxidative fission of the glycol under these conditions is fast and vigorous.

If an epoxide is the intermediate in the sulphuric acid oxidation, it must take part in the reaction as the conjugate acid which may be formulated as $R_2\overset{+}{C}\cdot C(OH)R_2$. If so, the subsequent course of the reaction must be determined by the solvent. In aqueous solution containing a low concentration of acid, hydration to glycol is favoured and consequently its oxidative fission will account for the greater part of the products. With a relatively high concentration of sulphuric acid, hydration might reasonably be expected to give place to rearrangement by the generally accepted mechanism for the pinacol–pinacolone change.

It has not yet been possible to obtain direct evidence of the sequence of reactions leading to the formation of an epoxide or its conjugate acid from an olefin. The simple transfer of an oxygen atom from chromic oxide to the olefin satisfies the overall requirements of the oxidation, but it is more satisfactory to assume the initial formation of a complex between the olefin and chromic acid. The most convincing support for this view is found in the close resemblance between the oxidising action of chromyl chloride and that of chromic oxide on olefins and paraffins (Cristal and Eilar, *J. Amer. Chem. Soc.*, 1950, **72**, 4353; Hobbs and Houston, *ibid.*, 1954, **76**, 1254). The addition of chromyl chloride probably occurs by electrophilic attack at the double bond. The application of these ideas to chromic acid or chromic oxide oxidations leads to an initial compound which can be represented as $R_2\overset{+}{C}\cdot CR_2\cdot OCrO_2$. The epoxide can be derived from this in an anhydrous medium by the loss of $Cr^{IV}O_2$. In aqueous sulphuric acid the formation of the conjugate acid of an epoxide may be an unnecessary assumption if the complex can undergo hydration and oxidative fission or rearrange under the influence of sulphuric acid by the usually accepted pinacol–pinacolone change.

Experimental

2 : 4-*Dimethylpent-2-ene* (I).—**2 : 4**-Dimethylpent-2-ene, b. p. 83—84°, n_D^{20} 1·4018, was obtained by refluxing **2 : 4**-dimethylpentan-3-ol with about four times its weight of oxalic acid (Wibaut *et al.*, *Rec. Trav. chim.*, 1943, **62**, 265, give b. p. 83·6°, n_D^{20} 1·4011). In several preparations a total of 185·6 g. was prepared from 346 g. of alcohol.

(a) ***Oxidation by chromic oxide: formation of* 2 : 3-*epoxy*-2 : 4-*dimethylpentane***. **2 : 4**-Dimethylpent-2-ene (66 g.) in carbon disulphide (100 ml.) was stirred in a 3-l. flask in ice–salt while chromic oxide (36 g.) in acetic anhydride (35 ml.) and carbon disulphide (300 ml.) was added dropwise during 2 hr. After a further 2 hr. a greenish-grey precipitate containing all the chromium was filtered off. The filtrate was shaken with saturated sodium carbonate solution and dried ($MgSO_4$; then K_2CO_3). After removal of the solvent and unchanged olefin, the main product was collected at 97—110° (14·2 g.) being essentially **2 : 3-*epoxy*-2 : 4-*dimethylpentane***. A further fractionation gave the pure epoxide (9·7 g.), b. p. 110—110·5°, n_D^{20} 1·3961—1·3963 (Found: C, 73·4; H, 12·3. $C_7H_{14}O$ requires C, 73·6; H, 12·4%).

For comparison, **2 : 3-epoxy-2 : 4-dimethylpentane** was prepared from the olefin by reaction with perbenzoic acid in ether; this had b. p. 110°, n_D^{20} 1·3956—1·3959. Both specimens had the same reactions and gave identical derivatives with the same m. p.s and no depression on admixture.

Reduction of the epoxide in ether by lithium aluminium hydride gives **2 : 4-dimethylpentan-2-ol**, b. p. 130—132°, n_D^{20} 1·4140—1·4141, characterised by its **3 : 5-dinitrobenzoate**, m. p. 70°. Huston and Smith (*J. Org. Chem.*, 1950, **15**, 1076) give m. p. 70°.

The epoxide reacts only very slowly with a solution of **2 : 4-dinitrophenylhydrazine** in 2% aqueous hydrochloric acid. A copious yellow precipitate of **2 : 2 : 3-*trimethylbutanal* 2 : 4-*dinitrophenylhydrazone***, m. p. 157—158°, was obtained immediately in warm 25% sulphuric acid (concentrations of sulphuric acid given in this paper are g. of acid in 100 g. of solution) (Found: C, 53·1; H, 6·3; N, 18·7. $C_{12}H_{16}O_4N_4$ requires C, 53·05; H, 6·2; N, 19·0%).

Shaking the epoxide with N-sulphuric acid gave **2 : 4-dimethylpentane-2 : 3-diol**, m. p. 58—59°, not depressed on admixture with a specimen prepared from **2 : 4-dimethylpent-2-ene**, in poor yield, by the action of *tert.*-butyl hydrogen peroxide and osmium tetroxide or, more

conveniently, by the action of hydrogen peroxide in formic acid, followed by alkaline hydrolysis. The structure of the glycol was confirmed by fission by periodic acid to acetone and *iso*butaldehyde which were separated and identified as 2 : 4-dinitrophenylhydrazones. The separation was effected by chromatography on silica with benzene–light petroleum, and this method was used for all the mixtures of aldehydes and ketones described below.

The glycol rearranges in warm 40% aqueous sulphuric acid containing 2 : 4-dinitrophenylhydrazine to give the 2 : 2 : 3-trimethylbutanal 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 159° (see above).

(b) *Oxidation by chromic acid in aqueous sulphuric acid: formation of* 2 : 2 : 3-*trimethylbutanoic acid.* 2 : 4-Dimethylpent-2-ene (25 g.) was stirred with 66% sulphuric acid (150 ml.), cooled in ice, while chromic oxide (65 g.) in water (50 ml.) was added dropwise. Oxidation became progressively slower and it was necessary to stir for 2 hr. after the addition was complete. Then carboxylic acids were removed by ether-extraction, separated from neutral material (1·2 g.) by alkali, and fractionally distilled to give *iso*butyric acid, b. p. 63—70°/22 mm. (2·3 g.) (*p*-toluidide, m. p. and mixed m. p. 108°), and ααβ-trimethylbutyric acid (4·7 g.), b. p. 96—97°/16 mm. (Found: C, 64·9; H, 10·4. Calc. for $C_7H_{14}O_2$: C, 64·6; H, 10·8%). The latter acid is reported to melt at 50° (Haller and Bauer, *Compt. rend*, 1909, **149**, 6; Richard, *Ann. Chim. Phys.*, 1910, **21**, 353) but our specimen did not solidify. Its amide, m. p. 130°, was identical with ααβ-trimethylbutyramide prepared as described by Haller and Bauer (Found: C, 64·9; H, 11·7; N, 10·8. Calc. for $C_7H_{15}ON$: C, 65·1; H, 11·7; N, 10·8%); the *p-toluidide* had m. p. 92° (Found: C, 77·0; H, 10·0; N, 6·3. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·7; N, 6·4%).

ααβ-Trimethylbutyric acid with lithium aluminium hydride in ether gave 2 : 2 : 3-trimethylbutan-1-ol, b. p. 55—60°/15 mm., n_D^{20} 1·4346, oxidised by *tert.*-butyl chromate to 2 : 2 : 3-trimethylbutanal (2 : 4-dinitrophenylhydrazone, m. p. 158—159° not depressed by a specimen obtained by rearrangement of 2 : 4-dimethylpentane-2 : 3-diol).

2-*Methylbut-2-ene* (VII).—2-Methylbut-2-ene, b. p. 38·6°, n_D^{20} 1·3870—1·3875, was prepared by slowly distilling 2-methylbutan-2-ol with 0·3% of its weight of iodine, and subsequently fractionating the mixture of olefins (438 g. from 784 g. alcohol, b. p. 31—39°) (yield, 114 g.).

Oxidation of the olefin in chloroform by perbenzoic acid gives 2 : 3-epoxy-2-methylbutane, b. p. 74—75°, which is reduced by lithium aluminium hydride to *tert.*-pentyl alcohol, b. p. 101—102°; a solution of 2 : 4-dinitrophenylhydrazine in 20% sulphuric acid gives an immediate precipitate of 2 : 4-dinitrophenylhydrazones of trimethylacetaldehyde, m. p. and mixed m. p. 208° in small yield, and of 3-methylbutan-2-one, m. p. and mixed m. p. 125°. The epoxide is hydrated by cold 5% hydrochloric acid to 2-methylbutane-2 : 3-diol, b. p. 75—76°/14 mm. The glycol was also prepared from ethyl lactate and methylmagnesium bromide and the two specimens had the same reactions: oxidative fission (periodic acid) gave acetaldehyde and acetone (separated and identified as 2 : 4-dinitrophenylhydrazones); rearrangement by warm 40% sulphuric acid containing 2 : 4-dinitrophenylhydrazine gave 3-methylbutan-2-one as the main product with some trimethylacetaldehyde, both isolated as 2 : 4-dinitrophenylhydrazones.

(i) *Oxidation by chromic oxide: formation of* 2 : 3-*epoxy-2-methylbutane and other products.* 2-Methylbut-2-ene (60 g.) in carbon disulphide (100 ml.) was oxidised by chromic oxide (50 g.) in acetic anhydride (50 ml.) and carbon disulphide under the conditions described on p. 1361. After removal of the solvent and unchanged olefin, 2 : 3-*epoxy-2-methylbutane*, b. p. 72—74°, n_D^{20} 1·3880—1·3887 (1·3 g.), was collected together with high-boiling material (A). In another oxidation, from 64 g. of olefin, 2·6 g. of epoxide were obtained (Found: C, 69·3; H, 11·9. $C_5H_{10}O$ requires C, 69·7; H, 11·7%). The identity was established by comparison with the epoxide and its derivatives prepared by the action of perbenzoic acid.

The material (A) was treated with water to remove acetic anhydride and on distillation gave 2-methylbutane-2 : 3-diol and a mixture of carbonyl compounds (1·6 g.), b. p. 30—56°/19 mm., n_D^{20} 1·4170—1·4196, which was resolved by chromatography of the 2 : 4-dinitrophenylhydrazones in silica (eluant benzene–light petroleum) into trimethylacetaldehyde in small amount, 3-methylbut-3-en-2-one, 3-methylbutan-2-one, and 3-methylbut-2-enal. These were identified by comparison with authentic specimens and the order given is that of their elution from silica. 3-Methylbut-3-en-2-one, b. p. 97°, n_D^{20} 1·4240, prepared by slowly distilling 3-hydroxy-3-methylbutan-2-one with toluene-*p*-sulphonic acid was characterised as 2 : 4-*dinitrophenylhydrazone*, orange needles (from ethyl acetate), m. p. 189—190° (Found: C, 49·8; H, 4·3; N, 21·5. $C_{11}H_{12}O_4N_4$ requires C, 50·0; H, 4·6; N, 21·3%). 3-Methylbut-2-enal, b. p. 126—130°, n_D^{20} 1·4543 (Fischer *et al.*, *Ber.*, 1931, **65**, 30, record b. p. 132—133°, n_D^{20} 1·4526), from the oxidation of 3-methylbut-2-en-1-ol with *tert.*-butyl chromate gave a 2 : 4-*dinitrophenylhydrazone*, m. p.

181·5° (Found: C, 50·2; H, 4·8%). The aldehyde is oxidised by chromic acid in dilute sulphuric acid to β-methylcrotonic acid, m. p. and mixed m. p. 70°.

(ii) *Oxidation by chromic acid in aqueous sulphuric acid: formation of 3-methylbutan-2-one.* The olefin (12·5 g.) was stirred with 55% sulphuric acid (45 ml.) at 0° while chromic oxide (28·5 g.) in 55% sulphuric acid (200 ml.) was added dropwise. The neutral product was 3-methylbutan-2-one (1·4 g.), b. p. 94—97° (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 126°).

2 : 3-*Dimethylbut*-1-*ene* (V).—This olefin, b. p. 55·6—55·8°, n_D^{20} 1·3899, was obtained as the lower-boiling constituent of the product of the dehydration of 2 : 3-dimethylbutan-2-ol (*J.*, 1954, 4200). It was distilled over sodium immediately before use.

(a) *Oxidation by chromic oxide: formation of* 1 : 2-*epoxy*-2 : 3-*dimethylbutane and* 3-*methylbutan*-2-*one.* (i) 2 : 3-Dimethylbut-1-ene (44 g.) was oxidised by chromic oxide (50 g.) in acetic anhydride (300 ml.) and the volatile products were distilled out of the mixture at 15 mm. into cold traps (solid carbon dioxide–acetone) until acetic anhydride began to distil. The distillate was diluted with ether and washed with water and aqueous potassium carbonate (acetone was present in the aqueous washings). Distillation through a column gave the following fractions after removal of solvent and unchanged olefin: (*a*) b. p. 56—80°, n_D^{20} 1·3890—1·3926, 0·6 g.; (*b*) b. p. 82—96°, n_D^{20} 1·3930—1·3967, 4·3 g.; (*c*) residue 0·4 g. The greater part of fraction (*b*) distilled at 94—97°, had n_D^{20} 1·3952—1·3960, and consisted of 1 : 2-epoxy-2 : 3-dimethylbutane, b. p. 95—96°, n_D^{20} 1·4020, and 3-methylbutan-2-one, b. p. 94°, n_D^{20} 1·3887. This was established by the following reactions: (*a*) A portion shaken for 2 days with 0·3N-hydrochloric acid gave 3-methylbutan-2-one, b. p. 90—100° (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 124°), and 2 : 3-dimethylbutane-1 : 2-diol, b. p. 90—93°/15 mm.; the glycol was rearranged by aqueous sulphuric acid to 2 : 3-dimethylbutanal (2 : 4-dinitrophenylhydrazone m. p. and mixed m. p. 125°), and on oxidation gave 3-methylbutan-2-one. (*b*) A warm solution of 2 : 4-dinitrophenylhydrazine in 25% sulphuric acid gave an immediate yellow precipitate from which 2 : 3-dimethylbutanal 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 125°, was readily isolated. (*c*) Reduction by lithium aluminium hydride in boiling ether and reaction of the alcohols thus formed with 3 : 5-dinitrobenzoyl chloride in pyridine gave two esters separated by chromatography on alumina; the less strongly adsorbed was identical with the 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 107—108°, of 2 : 3-dimethylbutan-2-ol; the more strongly adsorbed was the ester, m. p. and mixed m. p. 78°, of 3-methylbutan-2-ol.

(ii) 2 : 3-Dimethylbut-1-ene (51 g.) was oxidised by chromic oxide (45 g.) in acetic anhydride (350 ml.) with the difference that water was added to hydrolyse the acetic anhydride and to convert any epoxide into glycol. The neutral product was separated into the following fractions: (*a*) b. p. 89—100°, n_D^{20} 1·390—1·3963, 0·9 g.; (*b*) b. p. 110—118°, n_D^{20} 1·4030—1·4170, 0·5 g.; (*c*) b. p. 40—60°/25 mm., n_D^{20} 1·4190—1·4198, 0·7 g.; (*d*) b. p. 70—73°/25 mm., n_D^{20} 1·4205—1·4207, 1·2 g.; (*e*) b. p. 94°/10 mm., n_D^{20} 1·4320—1·4360, 4·9 g. Fraction (*e*) is essentially 2 : 3-dimethybutane-1 : 2-diol and was identified by the reactions enumerated earlier. 2 : 3-Dimethylbutanal and 3-methylbutan-2-one were recognised as present in fractions (*a*) and (*b*), by isolation of dinitrophenylhydrazones and by reduction to the corresponding alcohols. From fractions (*c*) and (*d*) the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 195°, of 2 : 3-dimethylbut-2-enal was readily obtained.

(b) *Oxidation by chromic acid in aqueous sulphuric acid: formation of αβ-dimethylbutyric acid.* 2 : 3-Dimethylbut-1-ene (10·7 g.) and 50% sulphuric acid (100 ml.) were stirred and cooled in ice while chromic oxide (20 g.) in 50% sulphuric acid (300 ml.) was added dropwise. The neutral product boiled at 92—100° and consisted essentially of 3-methylbutan-2-one (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 125°). The acid product was αβ-dimethylbutyric acid, b. p. 95—96°/18 mm., n_D^{20} 1·4141—1·4146 (1·2 g.) (amide, m. p. and mixed m. p. 130°; *p*-phenylphenacyl ester, m. p. and mixed m. p. 74°).

2 : 3-Dimethylbutane-1 : 2-diol (5·5 g.) in 50 ml. of 50% aqueous sulphuric acid, oxidised by chromic acid in 50% sulphuric acid, gave 3-methylbutan-2-one. There was no evidence of the formation of αβ-dimethylbutyric acid or of any other product.

Oct-1-*ene.*—This olefin was a gift from the Anglo-Iranian Oil Co. Ltd. It was refluxed over sodium and fractionated before each oxidation (b. p. 122°, n_D^{20} 1·4095).

(i) *Oxidation by chromic oxide.* (a) In acetic acid: formation of 1-acetoxyoctan-2-one. A solution of oct-1-ene (121 g.) in acetic acid (200 ml.) was oxidised at 0° by the gradual addition of chromic oxide (55 g.) in acetic acid (500 ml.). From the neutral products 1-acetoxyoctan-2-one, m. p. and mixed m. p. 43°, was isolated from the fraction of b. p. 79—83°/13 mm. (2·8 g.)

and was further identified as its semicarbazone, m. p. and mixed m. p. 40°, and 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 159° (*J.*, 1954, 4200).

From the lower-boiling fraction, b. p. 70—110°/15 mm., oct-1-en-3-one was isolated as 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 124°, after chromatography on silica. Other carbonyl compounds were present in smaller amounts but none was isolated pure. The acidic products were not examined.

(b) In carbon disulphide and acetic anhydride. A cold solution of oct-1-ene (68·5 g.) in carbon disulphide (100 ml.) was oxidised by the gradual addition of chromic oxide (40 g.) in acetic anhydride (40 ml.) and carbon disulphide (200 ml.). Distillation of the neutral product gave a fraction, b. p. 58—74°/15 mm., n_D^{20} 1·4195—1·4260 (2·4 g.), from which oct-1-en-3-one was isolated as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 124°. The acid products (4·0 g.) distilled at 98—110°/13 mm., and had n_D^{20} 1·4180—1·4220. By fractional distillation, and crystallisation and chromatography of the *p*-toluidides, *N*-*p*-tolyl-hexanamide, m. p. 72°, and -heptanamide, m. p. 75°, were separated.

cyclo*Hexene.—Oxidation by chromic oxide: formation of* 1 : 2-*epoxy*cyclo*hexane. cyclo*Hexene (256 g.; b. p. 83°, n_D^{20} 1·4471) in carbon disulphide (300 ml.) was oxidised by chromic oxide (60 g.) in acetic anhydride (60 ml.) and carbon disulphide (200 ml.) under the conditions already described. The product was separated by distillation into unchanged olefin (230 g.), 1 : 2-epoxy*cyclo*hexane, b. p. 130—132°, n_D^{20} 1·4578 (1·3 g.), a fraction, b. p. 86—93°/50 mm., n_D^{20} 1·4844 (2·9 g.), consisting largely of *cyclo*hex-2-enone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 167°), and a residue (A) (0·6 g.). 1 : 2-Epoxy*cyclo*hexane was identified by conversion into *trans-cyclo*hexane-1 : 2-diol, m. p. and mixed m. p. 103—104°, and by reduction by lithium aluminium hydride to *cyclo*hexanol (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 113°). The residue (A) contained *cyclo*hexane-1 : 2-dione [2 : 4-dinitrophenylhydrazone, scarlet needles (from ethyl acetate), m. p. and mixed m. p. 228°] and a small amount of *cyclo*hex-2-enone, which were isolated and separated as 2 : 4-dinitrophenylhydrazones. Chromatography of a portion of (A) on alumina gave a small amount of white solid, m. p. 120°, which contains 58% of hydrolysable acetate group.

Oxidation of 1 : 2-*Epoxy*cyclo*hexane.*—A solution of the epoxide (1·0 g.) in light petroleum was oxidised by *tert.*-butyl chromate (from 0·5 g. of chromic oxide) in light petroleum. A brown precipitate was formed slowly and after 3 hr. at room temperature, aqueous solutions of acetic and oxalic acids were added till the precipitate dissolved. From the ether extract *cyclo*hexane-1 : 2-dione was isolated as its red bis-2 : 4-dinitrophenylhydrazone, m. p. 228°.

*cyclo*Hexane-1 : 2-diol under similar conditions also gave *cyclo*hexane-1 : 2-dione.

For comparison, *cyclo*hexane-1 : 2-dione was prepared by refluxing *cyclo*hexanone with selenium dioxide for 3 hr. It boiled at 101—102°/25 mm. and gave a bis-2 : 4-dinitrophenylhydrazone, red crystals (from acetone), m. p. 230—232°, identical in every respect with that from 1 : 2-epoxy*cyclo*hexane and from *cyclo*hexane-1 : 2-diol. Campbell and McCall (*J.*, 1950, 2870) describe the bis-2 : 4-dinitrophenylhydrazone, m. p. 233—234° (Found : C, 45·7; H, 3·3; N, 23·9. Calc. for $C_{18}H_{16}O_8N_8$: C, 45·7; H, 3·4; N, 23·7%).

Pent-2-ene.—The olefin was a commercial sample, refluxed over sodium and fractionated to give material of constant b. p. 36° and n_D^{20} 1·3800.

(a) *Oxidation by chromic oxide.* A solution of the olefin (64 g.) in carbon disulphide (100 ml.) was oxidised under the conditions described above by chromic oxide (40 g.) in acetic anhydride (40 ml.) and carbon disulphide (300 ml.). The main bulk of the neutral product (4·3 g.) boiled at 100—120° and consisted essentially of pent-3-en-2-one with a small amount of pentane-2 : 3-dione, separated as, and recognised by crystallisation of, their 2 : 4-dinitrophenylhydrazones (see below). A small amount (0·9 g.) of neutral material, b. p. 70—85°, was also obtained which may have contained 2 : 3-epoxypentane (b. p. 84°), but no evidence of its presence could be obtained.

(b) *Oxidation of* 2 : 3-*epoxypentane.* The epoxide (1·5 g.) in light petroleum (b. p. < 40°) was oxidised by the addition of *tert.*-butyl chromate (from 0·5 g. of chromic oxide) in light petroleum. The neutral product was treated directly with 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid, to give pentane-2 : 3-dione bis-2 : 4-dinitrophenylhydrazone, bronze red needles (from acetone), m. p. 274° (Found : C, 44·2; H, 3·5; N, 24·8. Calc. for $C_{17}H_{16}O_8N_8$: C, 44·4; H, 3·5; N, 24·4%). Heilbron, Jones, Smith, and Weedon (*J.*, 1946, 57) give m. p. 280—281°.

Oxidation of 2 : 3-epoxypentane or pentane-2 : 3-diol by chromic oxide in carbon disulphide and acetic anhydride also gave pentane-2 : 3-dione.

For comparison and identification, pentane-2 : 3-dione was prepared by refluxing pentan-2-one (24 g.) with selenium dioxide (10 g.) for 2 hr. A mixture, b. p. 100—110° (21·5 g.), of diketone and unchanged ketone was obtained. It was sufficient for the present work to convert the mixture into 2 : 4-dinitrophenylhydrazones which were separated by taking advantage of the sparing solubility of the derivative of the dione in benzene : this is best purified by extraction with acetone (Soxhlet) and has m. p. 274°.

Preparation of Pent-3-en-2-one.—Pent-3-en-2-ol, b. p. 122°, n_D^{20} 1·4276, was oxidised by *tert.*-butyl chromate in light petroleum to give pent-3-en-2-one, b. p. 120—122°, n_D^{20} 1·1441; Alexander and Coraor (*J. Amer. Chem. Soc.*, 1951, **73**, 2721) give b. p. 121—122°, n_D^{20} 1·4377. The 2 : 4-dinitrophenylhydrazone formed deep red crystals, m. p. 157; Jones and Whiting (*J.*, 1949, 1428) give m. p. 158—159°.

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Steroids. Part IX. The Catalytic Hydrogenation of 3α-Substituted Δ⁵-Steroids.*

By J. R. LEWIS and C. W. SHOPPEE.

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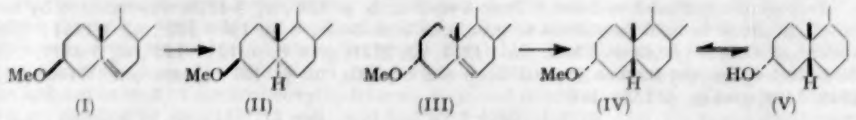
The influence of a 3α-substituent on the stereochemical course of catalytic hydrogenation of a steroid 5 : 6-double bond has been examined, and found to lead to the preferential, and sometimes apparently exclusive, formation of coprostane derivatives. The effect of the following 3α-orientated substituents has been examined : OH, OMe, OAc, Cl, Br, NHMe, NHAc, and NMe_3; the results suggest that the bulkier the axial 3α-substituent, the larger is the proportion of coprostane derivative formed.

CATALYTIC hydrogenation of 3β-substituted Δ⁵-steroids yields mainly saturated steroids of the A/B-*trans*-series; thus, cholest-5-ene affords cholestane (Mauthner, *Monatsh.*, 1906, **27**, 421), whilst cholesterol gives cholestan-3β-ol (Willstätter and Mayer, *Ber.*, 1908, **41**, 2199), cholesteryl chloride gives 3β-chlorocholestane (Mauthner, *Monatsh.*, 1909, **30**, 635; Windaus and Hossfeld, *Z. physiol. Chem.*, 1925, **145**, 177; Ruzicka, Goldberg, and Wirz, *Helv. Chim. Acta*, 1935, **18**, 998; Shoppee, *J.*, 1946, 1147), cholesteryl bromide gives 3β-bromocholestane (Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705), and 3β-dimethylaminocholest-5-ene gives 3β-dimethylaminocholestane (Haworth and Dodgson, *J.*, 1952, 67; Haworth, McKenna, and Powell, *J.*, 1953, 1110; Šorm, Labler, and Cerny, *Chem. Listy*, 1953, **47**, 418). These products are probably accompanied by small quantities of the saturated steroids of the 5-epimeric A/B-*cis*-series; thus Reichstein, Lardon, and Wenner (*Helv. Chim. Acta*, 1941, **24**, 955; 1944, **27**, 24) by hydrogenation of dehydro-*epi*androsterone acetate with platinum–acetic acid obtained *iso*androsterone acetate accompanied by 10—15% of 3β-acetoxy-5β-androstan-17-one [= 3β-acetoxy*ætio*cholan-17-one]. Until recently, the hydrogenation of 3β-substituted Δ⁵-steroids has been subject to some difficulty in regard to completion of reduction; Hershberg, Oliveto, Rubin, Staeudle, and Kuhlen (*J. Amer. Chem. Soc.*, 1951, **73**, 1144) found, however, that the hydrogenation was catalysed by traces of strong acids. The catalytic effect is determined by the strength of the acid; thus, weak acids with $pK > 3$, *e.g.*, acetic acid and benzoic acid, were ineffective, whilst strong acids with $pK < 3$, *e.g.*, perchloric acid, sulphuric acid, hydrogen bromide, and hydrogen chloride, were efficient catalysts. Cholesterol by hydrogenation with platinum–ethyl acetate in the presence of traces of perchloric acid rapidly gave 90% of cholestan-3β-ol, which was accompanied by 3·5% of coprostan-3β-ol.

* Part VIII, *J.*, 1954, 3422.

There appears to be little information in the literature relating to the hydrogenation of 3α-substituted Δ^5-steroids, and we have made a study of the catalytic reduction of various 3α-substituted cholest-5-enes. Whereas hydrogenation of cholesteryl methyl ether (I) with platinum–acetic acid gave 3β-methoxycholestane (II) (Wagner-Jauregg and Werner, *Z. physiol. Chem.*, **1932**, **213**, 119), hydrogenation of *epi*cholesteryl methyl ether (III) with



(I) (II) (III) (IV) (V)

platinum–methanol in the presence of a trace of hydrogen bromide gave 3α-methoxycoprostane (IV) as the sole product. The 3α-ether was shown by mixed m. p. and the infrared spectrum to be identical with a specimen prepared by methylation of coprostan-3α-ol (V) with potassium and methyl iodide in benzene, and was demethylated to coprostan-3α-ol (V) (Lewis and Shoppee, following paper).

Further experimentation showed that hydrogenation of *epi*cholesteryl methyl ether with platinum in methanol or ethyl acetate gave 3α-methoxycoprostane provided that reduction was promoted by traces of perchloric acid or sulphuric acid; with platinum in ethyl acetate–acetic acid, or in ethanol in the presence of potassium hydroxide (Wilds, Johnson, and Sutton, *J. Amer. Chem. Soc.*, **1950**, **72**, 5524; Yashin, Rosenkranz, and Djerassi, *ibid.*, **1951**, **73**, 4654), or in methanol–piperidine (Mancera, Ringold, Djerassi, and Sondheimer, *ibid.*, **1953**, **75**, 1286), reduction did not occur.

We have also found that *epi*cholesteryl acetate by hydrogenation with platinum–methanol–hydrogen bromide gives as the sole crystalline product 3α-acetoxycoprostane, converted by alkaline hydrolysis into coprostan-3α-ol. The hydrogenation of *epi*cholesterol using platinum in ether at 3 atm. has been reported by Marker, Oakwood, and Crooks (*ibid.*, **1936**, **58**, 481) to give a quantitative yield of cholestan-3α-ol, and more recently Fieser (*ibid.*, **1953**, **75**, 4377) confirmed his isolation of *epi*cholesterol, produced from cholesterol by oxidation with sodium dichromate in benzene–acetic acid *via* an intermediate cyclic 3α : 5α-chromate, by hydrogenation with platinum–ethyl acetate–perchloric acid in 35% yield to cholestan-3α-ol. Examination of the hydrogenation of *epi*cholesterol with platinum in methanol or ethyl acetate in the presence of various promoters showed that the product in all cases was a mixture of coprostan-3α-ol, m. p. 114—115°, and cholestan-3α-ol, m. p. 186°. Table 1 shows the proportions of these compounds formed, expressed as a percentage of the total product. The compounds constituting the small proportion of other products were eluted from columns of aluminum oxide with pentane; they probably consist, from hydrogenations in methanol, of cholestane, coprostane, 3α-methoxycholestane, and 3α-methoxycoprostane, and, from hydrogenations in ethyl acetate, of cholestane, coprostane, 3α-acetoxycholestane, and 3α-acetoxycoprostane.

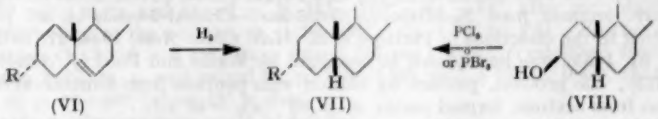
TABLE 1

Promoter	Cholestan-3α-ol (%)	Copro-stan-3α-ol (%)	Other products (%)	Promoter	Cholestan-3α-ol (%)	Copro-stan-3α-ol (%)	Other products (%)
In methanol.				*In ethyl acetate.*			
Hydrogen bromide	41	55	4·4	Hydrogen bromide	40	51	9·3
Perchloric acid ...	46	49	6·5	Perchloric acid ...	40	51	8·8
Sulphuric acid ...	37	48	15·5	Sulphuric acid ...	39	50	11·2
Hydrogen iodide...	No reduction*		—	Acetic acid	No reduction		—
Acetic acid	No reduction		—				

These results recall the remarkable influence of 11-hydroxyl groups on the stereochemical course of hydrogenation of 3-keto-Δ^4-steroids; whereas the presence of an 11β-hydroxyl group leads to 99% yields of 3-ketones of the A/B-*trans*-series (Shoppee and Reichstein, *Helv. Chim. Acta*, **1941**, **24**, 352; Pataki, Rosenkranz, and Djerassi, *J. Biol. Chem.*, **1952**, **195**, 791), the presence of an 11α-hydroxyl group leads to high yields of 3-ketone(s) of the A/B-*cis*-series (Mancera, Ringold, Djerassi, Rosenkranz, and Sondheimer, *J. Amer. Chem.*

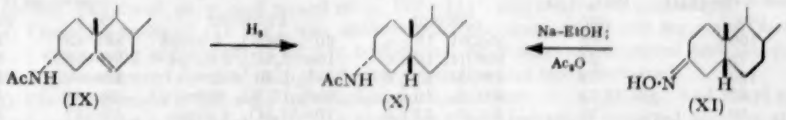
Soc., 1953, **75**, 1286) and can also modify the normal course of reduction of a Δ^{14}-linkage to yield C/D-*trans*-steroids by furnishing up to 50% of the epimeric C/D-*cis*-compound (Kuno Meyer, *Helv. Chim. Acta*, 1949, **32**, 1599).

A 3α-substituent is thus able to influence the stereochemical course of hydrogenation of a 5 : 6-double bond. Because ring A is a chair form in cholest-5-enes (Elks and Shoppee, *J.*, 1953, 241), a 3α-substituent possesses the axial conformation (Evans and Shoppee, *J.*, 1953, 540), and is therefore able to compel preferential adsorption of the β-face, rather than the normally more accessible α-face, of the steroid molecule on to the surface of the catalyst, with subsequent transfer of hydrogen leading to a coprostane derivative. The above results suggest that the bulkier the 3α-substituent, the larger the proportion of the coprostane derivative formed; we therefore examined the hydrogenation of *epi*cholesteryl chloride (VI; R = Cl), *epi*cholesteryl bromide (VI; R = Br), 3α-acetamidocholest-5-ene (IX), and 3α-dimethylaminocholest-5-ene (XII).



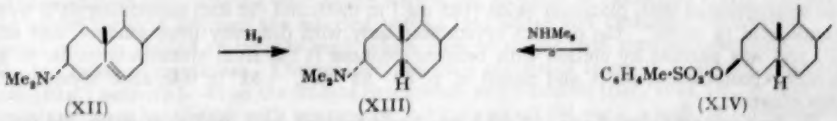
(VI) (VII) (VIII)

Hydrogenation of *epi*cholesteryl chloride (VI; R = Cl) with platinum–ethyl acetate–perchloric acid gave, as the sole product, 3α-chlorocoprostane (VII; R = Cl), which was identical with the compound previously obtained from coprostan-3β-ol (VIII) by treatment with phosphorus pentachloride (Bridgewater and Shoppee, *J.*, 1953, 1709). Similarly, hydrogenation of *epi*cholesteryl bromide (VI; R = Br) under similar conditions yielded coprostane accompanied by 3α-bromocoprostane, m. p. 80—82°, $[\alpha]_D$ +33° (VII; R = Br), which gave no depression by admixture with the product, m. p. 80°, $[\alpha]_D$ +27·5°, previously prepared in poor yield from coprostan-3β-ol (VIII) by reaction with phosphorus pentabromide (Bridgewater and Shoppee, *loc. cit.*).



(IX) (X) (XI)

Similar stereochemical behaviour is observed when 3α-substituents of the form OR are replaced by those of the form NHR or NR_2. Dr. G. H. R. Summers has found that hydrogenation of 3α-acetamidocholest-5-ene (IX) with platinum–acetic acid–ether yields 3α-acetamidocoprostane (X), identical with the principal product (after acetylation) of the reduction of coprostan-3-one oxime (XI) with sodium–ethanol (Evans, Shoppee, and Summers, *Chem. and Ind.*, 1954, 1535). We have likewise found (Pierce, Richards, Shoppee, Stephenson, and Summers, *J.*, 1955, 694) that 3α-dimethylaminocholest-5-ene (XII) by hydrogenation with platinum–acetic acid affords 3α-dimethylaminocoprostane (XIII); this reaction has also been observed by Haworth, McKenna, and Powell (*J.*, 1953, 1110), and by Šorm, Labler, and Czerny (*Chem. Listy*, 1953, **47**, 48) who lately have correctly interpreted their original experiments which included the preparation of the tertiary base (XIII) from 3β-toluene-*p*-sulphonyloxycoprostane (XIV) by solvolysis with dimethylamine, in a more recent paper (*Chem. Listy*, 1954, **48**, 1058).



(XII) (XIII) (XIV)

Analogous observations have recently been recorded in the hydrogenation with platinum–acetic acid of 3α-*N*-methylaminopregna-5 : 20-diene and of 3α-dimethylaninopregn-5-ene (as XII), which both furnish (after methylation in the former case)

3α-*NN*-dimethylaminopregnane (as XIII) (Haworth, McKenna, and Powell, *loc. cit.*; Pierce *et al.*, *loc. cit.*). A conspectus of the foregoing results is provided by Table 2, which shows the approximate proportions of saturated steroids of the A/B-*cis*- and the A/B-*trans*-series formed by catalytic hydrogenation of various 3α-substituted Δ^5-steroids.

TABLE 2.

3α-Substituent	OH	OMe	OAc	Cl	Br	NHMe	NHAc	NMe_2
A/B-*cis*-Steroid (%)	~50	>90	>90	>90	~40 *	~100	>90	~100
A/B-*trans*-Steroid (%)	~40	None isolated						

* Together with *ca.* 60% of coprostane.

EXPERIMENTAL.

For general details see *J.*, 1955, 694. Specific rotations were determined in $CHCl_3$; infra-red absorption spectra were measured in CS_2 on a Perkin-Elmer double-beam instrument.

3α-Methoxycoprostane from 3α-Methoxycholest-5-ene.—Cholest-5-en-3α-ol, m. p. 141°, prepared according to the directions of Plattner *et al.* (*Helv. Chim. Acta*, 1944, **27**, 1872; 1947, **30**, 1454; 1948, **31**, 1455), was methylated as described by Wallis and Ford (*J. Amer. Chem. Soc.*, 1937, **59**, 1415); the product, purified by elution with pentane from aluminium oxide and by crystallisation from acetone, formed plates, m. p. 88°, $[\alpha]_D$ −46°.

(*a*) 3α-Methoxycholest-5-ene (189 mg.), dissolved in methanol (50 c.c.) containing 48% hydrobromic acid (4 drops), was shaken with platinum oxide (35 mg.) in an atmosphere of hydrogen until absorption ceased. The usual working up gave an oil (176 mg.), which by crystallisation from acetone gave 3α-*methoxycoprostane*, m. p. 87—88°, $[\alpha]_D$ +36° (*c*, 1·0) [Found: (after drying at 45°/0·01 mm. for 4 hr.): C, 83·3; H, 12·5. $C_{28}H_{50}O$ requires C, 83·5; H, 12·5%], whose infra-red absorption spectrum will be discussed by Dr. J. E. Page in a forthcoming paper. In another experiment, 3α-methoxycholest-5-ene (500 mg.) yielded 3α-methoxycoprostane (470 mg.), m. p. 88° after crystallisation from acetone.

(*b*) Similar experiments were made as follows:

3α-Methoxycholest-5-ene (III) (mg.)	PtO_2,H_2O (mg.)	Solvent	Promoter	3α-Methoxycoprostane (IV) m. p.	mg.
100	75	MeOH, 15 c.c.	60% $HClO_4$, 4 drops	86—88°	91
75	35	MeOH, 15 c.c.	10N-H_2SO_4, 3 drops	87—88	70
120	72	EtOAc, 15 c.c.	48% HBr, 4 drops	87—88	115
62	73	EtOAc, 10 c.c.	60% $HClO_4$, 4 drops	86—88	57
90	85	EtOAc, 12 c.c.	10N-H_2SO_4, 4 drops	87—88	85

The specimens of 3α-methoxycoprostane were crystallised from acetone and gave no depressions by admixture with authentic 3α-methoxycoprostane, m. p. 88°, $[\alpha]_D$ +32° (see Lewis and Shoppee, following paper), whilst the infra-red adsorption spectra were identical.

(*c*) 3α-Methoxycholest-5-ene (350 mg.), in ethanol (50 c.c.) containing finely powdered potassium hydroxide (80 mg.) shaken with platinum oxide (97 mg.) in hydrogen, failed to absorb hydrogen. The product was unchanged starting material, m. p. 86—88°, depressed on admixture with 3α-methoxycoprostane to 50°. A repetition gave the same result.

(*d*) 3α-Methoxycholest-5-ene (100 mg.), in methanol (10 c.c.) containing piperidine (2 c.c.) shaken with platinum oxide (30 mg.) in hydrogen, failed to absorb hydrogen and furnished unaltered starting material, m. p. and mixed m. p. 87—88°.

(*e*) 3α-Methoxycholest-5-ene (85 mg.), in ethyl acetate (15 c.c.) containing acetic acid (15 drops) shaken with platinum oxide (47 mg.), failed to take up hydrogen and gave starting material, m. p. and mixed m. p. 87—88°.

3α-Acetoxycoprostane from 3α-Acetoxycholest-5-ene.—(*a*) 3α-Acetoxycholest-5-ene (60 mg.) was hydrogenated with platinum oxide (163 mg.) in methanol (10 c.c.) containing 48% hydrobromic acid (3 drops); the product crystallised only with difficulty from ethanol, had m. p. 81°, and was purified by elution with benzene–pentane (1 : 9) from aluminium oxide, to give 3α-acetoxycoprostane, m. p. and mixed m. p. 82—83°, $[\alpha]_D$ +52° (*c*, 0·4), after crystallisation from ethanol.

(*b*) 3α-Acetoxycholest-5-ene (52 mg.) was hydrogenated with platinum oxide (94 mg.) in methanol (15 c.c.) containing 60% perchloric acid (5 drops). Similar purification gave 3α-acetoxycoprostane, m. p. and mixed m. p. 83°, $[\alpha]_D$ +44° (*c*, 0·4).

(*c*) 3α-Acetoxycholest-5-ene (54 mg.) was hydrogenated with platinum oxide (55 mg.) in ethyl

acetate (10 c.c.) containing 60% perchloric acid (4 drops) to give after similar purification 3α-acetoxycoprostane (47 mg.), m. p. and mixed m. p. 81—83°.

(*d*) 3α-Acetoxycholest-5-ene (47 mg.) was hydrogenated with platinum oxide (40 mg.) in ethyl acetate (10 c.c.) containing 10N-sulphuric acid (5 drops); similar purification gave 3α-acetoxycoprostane (42 mg.), m. p. and mixed m. p. 80—82°.

The specimens of 3α-acetoxycoprostane (150 mg.) were hydrolysed with hot 5% methanolic potassium hydroxide to give, after the usual working up, a solid, m. p. 110—112°, after crystallisation from methanol; recrystallisation afforded coprostan-3α-ol, m. p. and mixed m. p. 113—114°, $[\alpha]_D$ +29° (*c*, 0·44).

Coprostan-3α-ol and Cholestan-3α-ol from Cholest-5-en-3α-ol.—(*a*) Cholest-5-en-3α-ol (50 mg.) was hydrogenated with platinum oxide (76 mg.) in methanol (15 c.c.) containing 48% hydrobromic acid (4 drops). After filtration from the catalyst, the solution was kept over anhydrous potassium carbonate for 0·5 hr., refiltered, and evaporated in a vacuum. The residual oil (48 mg.) was chromatographed on aluminium oxide (4 g.). Elution with pentane (3 × 5 c.c.) gave a little oil (2 mg.), but use of benzene–pentane (1 : 3; 4 × 4 c.c.) gave cholestan-3α-ol (19 mg.), m. p. and mixed m. p. 183—185°, $[\alpha]_D$ +34°, after recrystallisation from acetone, characterised as the acetate, m. p. 94—95°, $[\alpha]_D$ +33° (*c*, 1·1). Further elution with benzene–pentane (1 : 3; 8 × 5 c.c.) gave an oil (25 mg.) which crystallised from acetone to yield coprostan-3α-ol, m. p. and mixed m. p. 110—112°, $[\alpha]_D$ +29° (*c*, 0·44), characterised as the acetate, m. p. 87—88°, $[\alpha]_D$ +43° (*c*, 0·4).

(*b*) Similar experiments were made as follow:

Cholest-5-en-3α-ol (mg.)	PtO_2,H_2O (mg.)	Solvent	Promoter	Coprostan-3α-ol m. p.	Coprostan-3α-ol mg.	Cholestan-3α-ol m. p.	Cholestan-3α-ol mg.
67	104	MeOH, 15 c.c.	60% $HClO_4$, 4 drops	109—111°	24	182—185°	22
45	69	MeOH, 12 c.c.	10N-H_2SO_4, 4 drops	111—112 *	25	182—183 *	19
50	72	EtOAc, 15 c.c.	48% HBr, 4 drops	109—110	22	183—184	17
54	70	EtOAc, 15 c.c.	60% $HClO_4$, 3 drops	111—112	29	184	23
40	50	EtOAc, 12 c.c.	10N-H_2SO_4, 3 drops	110—111	15	182—183	12

* Elution with pentane gave 8 mg. of uncrystallisable material.

(*c*) Cholest-5-en-3α-ol (66 mg.) was shaken with platinum oxide (107 mg.) and methanol (15 c.c.) containing 57% hydriodic acid (3 drops) in hydrogen for 1·5 hr.; no reduction took place and cholest-5-en-3α-ol, m. p. and mixed m. p. 140—141°, was recovered unchanged.

(*d*) Cholest-5-en-3α-ol (51 mg.) was shaken with platinum oxide (59 mg.) and methanol (15 c.c.) containing acetic acid (3 c.c.) in hydrogen; no absorption occurred and the starting material was recovered, having m. p. 140° after crystallisation from methanol.

(*e*) Cholest-5-en-3α-ol (55 mg.) was shaken with platinum oxide (51 mg.) and ethyl acetate (15 c.c.) containing acetic acid (3 c.c.) in hydrogen; no absorption occurred and the starting material was recovered, having m. p. 140—141° after crystallisation from methanol.

3α-Chlorocoprostane from 3α-Chlorocholest-5-ene.—3α-Chlorocholest-5-ene (m. p. 107°; 101 mg.) (Shoppee and Summers, *J.*, 1952, 1790) was hydrogenated with platinum oxide (120 mg.) in ethyl acetate (15 c.c.) containing 60% perchloric acid (4 drops). After 1 hr., the usual working up yielded an oil (98 mg.), which failed to crystallise. Chromatography on a column of aluminium oxide (5 g.) prepared in pentane gave by elution with pentane (5 c.c.) an oil (20 mg.); further elution with pentane (4 × 5 c.c.) afforded 3α-chlorocoprostane (79 mg.), m. p. 73°, $[\alpha]_D$ +33° (*c*, 0·5), after crystallisation from acetone. The specimen gave no colour with tetranitromethane–chloroform, and no m. p. depression on admixture with 3α-chlorocoprostane prepared from coprostan-3β-ol by treatment with phosphorus pentachloride (Bridgewater and Shoppee, *J.*, 1953, 1709).

3α-Bromocoprostane from 3α-Bromocholest-5-ene.—3α-Bromocholest-5-ene (m. p. 105°; 190 mg.) was hydrogenated under the conditions employed for the chloro-derivative; the reduction required 4 hr., and furnished an oil (189 mg.) giving a yellow colour with tetranitromethane–chloroform. The oil was shaken with a 2% solution of chromium trioxide in acetic acid at 60° for 0·75 hr., and the solution poured into water and extracted with ether. The neutral fraction yielded an oil (135 mg.), which gave no colour with tetranitromethane–chloroform but failed to crystallise. Chromatography on a column of specially activated aluminium oxide [10 g.; activity I—II on the scale of Brockmann and Schodder (*Ber.*, 1941, **74**, 73)], prepared in pentane, gave by elution with pentane (6 × 5 c.c.) an oil (81 mg.), which by crystallisation from acetone afforded coprostane, m. p. and mixed m. p. 66—70°; further elution with pentane (4 × 5 c.c.) gave an oil (47 mg.), which by crystallisation from acetone yielded pure *3α-bromocoprostane*, m. p. 80—82°, $[\alpha]_D$ +33° (*c*, 0·63) [Found (after drying at 50°/0·01 mm. for 3 hr.):

Br, 17·6. $C_{37}H_{47}Br$ requires Br, 17·7%], giving no colour with tetranitromethane–chloroform and no m. p. depression with a specimen, m. p. 80°, $[\alpha]_D$ +27·5°, previously thought to be impure because of poor analyses, prepared from coprostan-3β-ol by treatment with phosphorus pentabromide (Bridgewater and Shoppee, *loc. cit.*). M. p. depressions were observed with 3α-bromocholestane, m. p. 103° (Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705) and with 3β-bromocoprostane, m. p. 113° (Bridgwater and Shoppee, *loc. cit.*).

3α-Acetamidocoprostane from 3α-Acetamidocholest-5-ene [by G. H. R. Summers].—3α-Acetamidocholest-5-ene (m. p. 186—189°; 20 mg.) was hydrogenated with platinum oxide (10 mg.) in acetic acid–ether (1 : 1, 10 c.c.) containing 60% perchloric acid (1 drop). The uptake of hydrogen was complete after 0·5 hr. The product, an oil, was isolated in the usual way, and chromatographed on aluminium oxide (1·5 g.). Elution with pentane yielded an oil, whilst use of pentane–benzene (1 : 1) gave a solid, m. p. 210—214°, which after sublimation at 200—210°/0·02 mm. and crystallisation from acetone yielded 3α-acetamidocoprostane as plates, m. p. 214—217°, undepressed on admixture with authentic specimen but depressed to 190—120° by 3α-acetamidocholestane, m. p. 189° (Pierce *et al.*, *J.*, 1955, 694).

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University College of Swansea, University of Wales. [*Received, December 23rd*, 1954.]

Steroids. Part X. The Preparation of Unsaturated Steroids.*

By D. R. James, R. W. Rees, and C. W. Shoppee.

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A general method for introduction of unsaturation into the steroid nucleus is described. It involves the reaction sequence: $-CO\cdot CHR- \longrightarrow -CO\cdot CRBr- \longrightarrow -CH(OR')\cdot CRBr- \longrightarrow -CH{:}CR-$, and is exemplified by introduction of unsaturation at the 6 : 7-position.

It is shown by reference to the literature and to the present example, 7α-bromo-6β- and -6α-hydroxycholestan-3β-yl acetate, that pairs of *trans*- and *cis*-1 : 2-bromohydrins on treatment with zinc in ethanol furnish the same olefin in good yield and at apparently approximately similar rates. It is suggested that these reactions involve the conjugate base derived from either bromohydrin by the irreversible extraction of a bromonium ion by an atom of zinc in the rate-controlling stage.

Steroids with carbonyl groups at the various nuclear positions are relatively accessible substances, and readily afford α-bromo-ketones, which have been shown (Shoppee and Summers, *J.*, 1952, 1786, 1790) to furnish *vic*-halogenohydrins on reduction with lithium aluminium hydride or sodium borohydride. Since the reaction of *vic*-halogenohydrins and their derivatives with zinc to yield olefins has been shown to be general (Straus and Rohrbacher, *Ber.*, 1921, **54**, 40; Boord *et al.*, *J. Amer. Chem. Soc.*, 1930, **52**, 3396; 1931, **53**, 1505; 1932, **54**, 751; 1933, **55**, 3293), the sequence, $-CO\cdot CHR- \longrightarrow -CO\cdot CRBr- \longrightarrow -CH(OR')\cdot CRBr- \longrightarrow -CH{:}CR-$, should permit introduction of unsaturation at any position (other than Δ^8 and $\Delta^{8(14)}$) in the steroid nucleus.

We now report such introduction of unsaturation at the 6 : 7-position (cf. Garmaise and Shoppee, *J.*, 1953, 245). Since this work was commenced in 1951, the above reaction sequence has been used to give steroids unsaturated at the 2 : 3-position (Fieser and Dominguez, *J. Amer. Chem. Soc.*, 1953, **75**, 1704; Corey, *ibid.*, p. 4832; Fieser and Huang, *ibid.*, p. 4837), the 3 : 4-position (Fieser and Ettorre, *ibid.*, p. 1700; Fieser and Dominguez, and Fieser and Huang, *locc. cit.*), the 5 : 6-position (Mori, *J. Chem. Soc. Japan*, 1949, **70**, 303; Ueno, *J. Pharm. Soc. Japan*, 1952, **72**, 1622), the 9 : 11-position (Fried and Szabo,

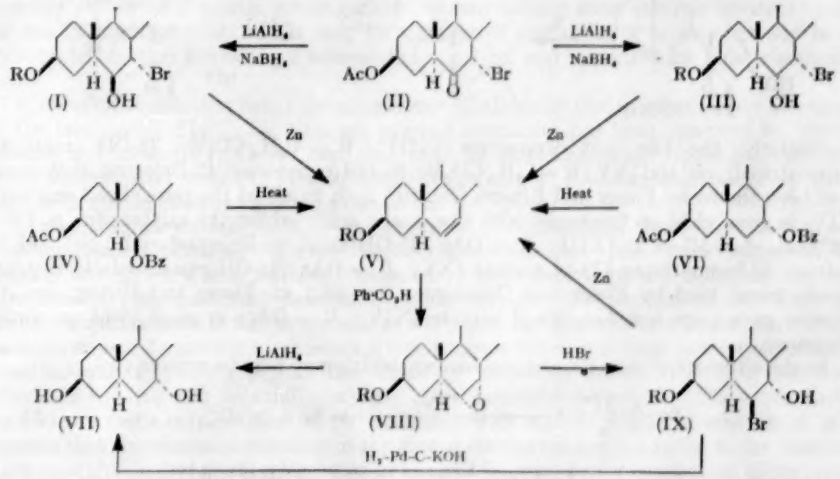
* Part IX, preceding paper.

J. Amer. Chem. Soc., **1953**, **75**, 2273), and the 11 : 12-position (Cornforth, Osbond, and Phillipps, *J.*, **1954**, 907; Elks, Phillipps, Taylor, and Wyman, *ibid.*, p. 1739).

7α-Bromo-6-oxocholestan-3β-yl acetate (II) by reduction with lithium aluminium hydride affords a mixture of epimeric 7α-bromocholestane-3β : 6-diols (I, III; R = H), converted by zinc and acetic acid in high yield into cholest-6-en-3β-ol (V; R = H). By use of sodium borohydride the 7α-bromo-ketone acetate (II) gives 7α-bromo-6β-hydroxycholestan-3β-yl acetate (I; R = Ac) and the 6α-epimer (III; R = Ac); *both* epimers on treatment with activated zinc in ethanol give cholest-6-en-3β-yl acetate (V; R = Ac), also obtained by acetylation of the alcohol (V; R = H), and hydrolysed thereto by treatment with lithium aluminium hydride. The alcohol was characterised by preparation of the benzoate and 3 : 5-dinitrobenzoate; the presence of a hydroxyl group in the alcohol and of an acetoxyl group in its acetate, and the presence of a *cis*-disecondary double bond, were confirmed by infra-red absorption spectroscopy. The acetate was shown by direct comparison to be identical with the materials obtained by Barton and Resenfelder (*J.*, 1949, 2459) and by Wintersteiner and Moore (*J. Amer. Chem. Soc.*, 1950, **72**, 1923) by pyrolysis of 6β-benzoyloxycholestan-3β-yl acetate (IV) and of 7α-benzoyloxycholestan-3β-yl acetate (VI) respectively. The physical constants of our samples of the alcohol, its acetate and benzoate, and those of Barton and Rosenfelder's and of Wintersteiner and Moore's samples are as follows:

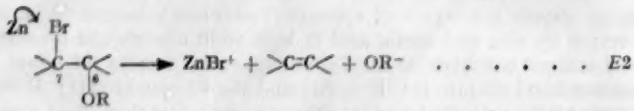
	Cholest-6-en-3β-ol		Acetate		Benzoate	
	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$	m. p.	$[\alpha]_D$
This work	124—126°	−88°	108°	−93°	132—133°	−85°
Barton and Rosenfelder ...	114—115	−92	103—105	−89	123—124	−75
Wintersteiner and Moore	129—131	−81	104—106	−88	128—129	−74

Cholest-6-en-3β-yl acetate (V) and perbenzoic acid give 6α : 7α-epoxycholestan-3β-yl acetate (VIII), converted by lithium aluminium hydride into cholestane-3β : 7α-diol (VII) (Wintersteiner and Moore, *J. Amer. Chem. Soc.*, 1943, **65**, 1503; Buser, *Helv. Chim. Acta*, 1947, **30**, 1379; Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, **71**, 2226). By

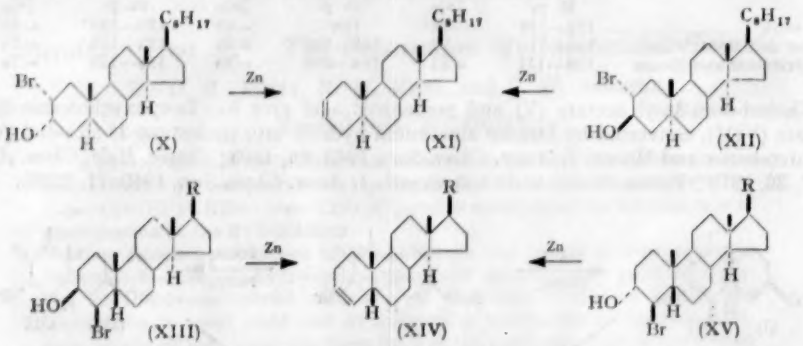


treatment with hydrogen bromide–acetic acid the 6α : 7α-epoxide (VIII) gives the 6β-bromo-7α-ol 3-acetate [IX; 6β-Br(axial)/7α-OH(axial) : *trans*] converted by zinc into cholest-6-en-3β-yl acetate (V), and hydrogenated by palladium to give cholestane-3β : 7α-diol (VII). The 6β-bromo-7α-ol 3-acetate (IX), by treatment with methanolic potassium hydroxide, regenerated (after acetylation) the 6α : 7α-epoxide (VIII).

Two mechanisms for ionic elimination reactions are in current use. In the present context the bimolecular mechanism involving synchronous processes may be written :

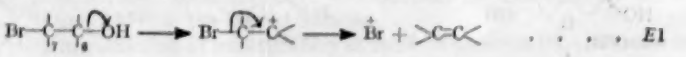


The geometrical condition for relatively ready bimolecular elimination is that the four reaction centres are coplanar and *trans*-orientated (Hughes, Ingold, *et al.*, *J.*, 1948, 2117; cf. Young, Pressman, and Coryell, *J. Amer. Chem. Soc.*, 1939, **61**, 1640; Winstein, Pressman, and Young, *ibid.*, p. 1645), which is satisfied by the bromohydrin [I; 6β-OH(axial)/7α-Br(axial) : *trans*]. A non-planar *cis*-orientation of the groups to be eliminated as in the bromohydrin [III; 6α-OH(equatorial)/7α-Br(axial) : *cis*] should energetically discourage, although not necessarily exclude,* the synchronous mechanism *E2*. Yet both bromohydrins readily furnish cholest-6-en-3β-ol (V; R = H). Other examples have been reported; thus Fieser and Dominguez (*loc. cit.*), using a mixture (m. p. 104°, $[\alpha]_D$ +25°) of 2α-bromocholestan-3α-ol, m. p. 117°, $[\alpha]_D$ +33° [X; 2α-Br(equatorial)/3α-OH(axial) : *cis*], and 3β-ol, m. p. 113°, $[\alpha]_D$ +12° [XII; 2α-Br(equatorial)/3β-OH(equatorial) : *trans*] (cf. Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 4832; Fieser and Huang, *loc. cit.*), obtained pure cholest-2-ene (XI) in good yield by brief treatment with zinc–acetic acid.



Similarly, the bile acid derivatives [XIII; R = $C_4H_8{\cdot}CO_2Me$: 3β-OH (axial)/4β-Br(equatorial) : *cis*] and [XV; R = $C_4H_8{\cdot}CO_2Me$: 3α-OH (equatorial)/4β-Br(equatorial) : *trans*] have been shown by Fieser and Ettorre (*loc. cit.*) both to afford the pure chol-3-enic ester (XIV) in good yield on treatment with zinc–acetic acid; whilst the mixture (m. p. 138—139°, $[\alpha]_D$ +58·5°) of 3β-[XIII; R = OAc : 3β-OH(axial)/4β-Br(equatorial) : *cis*] and 3α-hydroxy-4β-bromotestan-17β-yl acetate [XV; R = OAc : 3α-OH(equatorial)/4β-Br(equatorial) : *trans*] used by Fieser and Dominguez (*loc. cit.*; cf. Fieser and Huang, *loc. cit.*) likewise gave pure test-3-en-17β-yl acetate (XIV; R = OAc) in good yield on similar treatment.

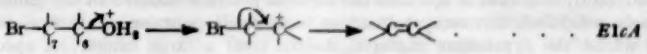
In the alternative unimolecular mechanism, which may here be written :



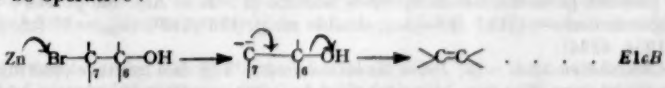
a rate-controlling heterolysis leads to a carbonium ion, which if sufficiently long-lived, will become planar, so that elimination of the bromine atom should be independent of the

* Cristol and Hause (*J. Amer. Chem. Soc.*, 1952, **74**, 2193) have shown that *trans*-11 : 12-dichloro-9 : 10-dihydro-9 : 10-ethanoanthracene on treatment with potassium hydroxide undergoes *cis*-dehydrohalogenation some ten times faster than the *cis*-11 : 12-dichloro-isomeride undergoes *trans*-dehalogenation; this is entirely due to the entropy of activation, which favours *cis*-elimination by a factor of 2000, since the *trans*-dehydrohalogenation requires an energy of activation lower by 4 kcal.

original geometry. If, however, elimination of the bromine atom occurs before the hydroxyl group has receded far enough to leave a planar ion, then *trans*-geometry will be preferred and coplanarity desirable. Such a mechanism seems improbable because the essential reagent appears to be the zinc since, as we have observed, the solvent can be changed without affecting the ease of elimination from both the *cis*- and the *trans*-bromohydrins (cf. Fieser and Ettorre, *loc. cit.*). This change of solvent from acetic acid to ethanol also appears to exclude a variant in which the rate-determining heterolysis involves the conjugate acid of the bromohydrin



We suggest that another variant (cf. Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell & Sons, London, 1953, 423), in which the rate-controlling step involves the irreversible extraction of a bromonium ion by an atom of zinc (cf. Ingold and Shoppee, *J.*, 1928, 371), may be operative:



The same intermediate carbanion might well be obtained from both bromohydrins, that carbanion derived directly from (I) (in which the lone pair destined to form the double bond can enter the octet of $C_{(6)}$ on the side opposite to that from which the hydroxyl anion departs) being also rapidly produced from (III) by inversion * at $C_{(7)}$ (cf. Roberts, Shoppee, and Stephenson, *J.*, 1954, 2705; Roberts and Shoppee, *ibid.*, p. 3418).

We find that the *trans*- (I) and the *cis*-bromohydrin acetate (III) are unchanged by zinc in ethanol at 50° for 45 hr.: after 3 hr. at ~78°, the *trans*-isomeride was completely converted into cholest-6-en-3β-yl acetate (V; R = Ac), whereas some of the *cis*-isomeride could be recovered; this suggests a small qualitative difference in the rates of dehydroxybromination, since after 6 hr. at ~78° both isomerides were completely converted into the olefin (V; R = Ac). The heterogeneous character of the reaction in the presence of zinc dust has prevented a kinetic investigation; we are seeking some suitable bivalent cation for use in place of zinc, which may be capable of extracting a bromonium ion in an appropiate medium furnishing a homogeneous system, and so permitting kinetic measurements.

It seems probable that dehalogenation of *vic*-dihalides by zinc in ethanol may also occur by the mechanism *E1cB*; for although product specificity has been observed by Young, Jasaitis, and Levanas (*J. Amer. Chem. Soc.*, 1937, **59**, 403), Cristol and Hause (*loc. cit.*) have found that *cis*- and *trans*-11 : 12-dichloro-9 : 10-dihydro-9 : 10-ethanoanthracene on treatment with zinc in ethanol yield the same olefin.

[*Added February 18th, 1955.*]—An example of elimination from *cis*- and *trans*-2 : 3-dimethanesulphonates of the sapogenin series has just been reported by Wendler and Slates (*Chem. and Ind.*, 1955, 167); both 2α[equatorial] : 3α[axial]- (A) and 2α[equatorial] : 3β[equatorial]-dimethanesulphonyloxy-5α : 22*a*-spirostan-12-one (B), by treatment with sodium iodide in acetone at 100°, give 5α : 22*a*-spirost-2-en-12-one. These reactions appear to involve mechanism *E1cB*, wherein the initial stage is the extraction of a methanesulphonyloxy-group as the cation by an iodide anion. The fact that both 2β[ax] : 3β[eq]- (C) and 2β[axial] : 3α[axial]-dimethanesulphonyloxy-5α : 22*a*-spirostan-12-one (D) are essentially unaffected by treatment with sodium iodide in acetone at 100° suggests that the *mutual* orientation of the groups eliminated is not a factor in the reaction. It seems probable that steric retardation at $C_{(2)}$ and $C_{(3)}$ may be the controlling factor, since the order of increasing steric hindrance is *trans*-2α : 3β[equatorial : equatorial] (A) < *cis*-2α : 3α[equatorial : axial] † (B) < *cis*-2β : 3β[axial : equatorial] ‡ (C) < *trans*-2β : 3α-[axial : axial] (D). Another example of a *cis*-elimination has been described by Djerassi

* An analogous inversion was envisaged by Cristol and Hause (*loc. cit.*).
† 1 : 2-Interactions with 1α-H and 5α-H.
‡ 1 : 2-Interactions with 4β-H and 10β-Me.

and Fishman (*Chem. and Ind.*, 1954, 1320) in which *cis*-2ξ : 3ξ-dimethanesulphonyloxy-22*a*-spirostan by treatment with sodium iodide in acetone furnishes 22*a*-spirost-2-ene.

Experimental

For general experimental directions see *J.*, 1954, 4224; $[\alpha]_D$ are in $CHCl_3$, and infra-red absorption spectra were determined in CS_2 on a Perkin-Elmer double-beam spectrometer.

Reduction of 7α-Bromo-6-oxocholestan-3β-yl Acetate.—(a) *With lithium aluminium hydride.* The 7α-bromo-ketone (m. p. 145°; 1 g.), dissolved in ether, was added to a solution of lithium aluminium hydride (200 mg.) in ether at 20°; after 0·25 hr. at 36° excess of the reagent was destroyed by addition of ice, and the neutral product isolated in the usual way. The resultant oil soon solidified, but recrystallisation from ether–pentane or acetone–pentane tended to give gels whilst the crystalline material melted over a large range. A specimen consisting of a mixture of 7α-bromocholestane-3β : 6β- and 3β : 6α-diol had m. p. 178—182° after softening, $[\alpha]_D$ −14° (*c*, 3·4) [Found (after drying at 60°/0·05 mm. for 3 hr.) : C, 67·6; H, 10·0. Calc. for $C_{27}H_{47}O_2Br$: C, 67·2; H, 9·8%]. Chromatographic separation of the diols was unsuccessful.

(b) *With sodium borohydride.* Reduction of the 7α-bromo-ketone and chromatography of the product gave the 7α-bromo-6β-ol acetate (I; R = Ac), m. p. 178°, $[\alpha]_D$ −24°, and the 6α-epimer acetate (III; R = Ac), double m. p. 136°/145°, $[\alpha]_D$ −9° (cf. James and Shoppee, *J.*, 1954, 4224).

Cholest-6-en-3β-ol.—(a) *From the mixed diols.* The diol mixture (660 mg.) was heated under reflux with zinc dust in acetic acid for 1 hr.; after cooling, water was added and the product extracted with ether, washed to neutrality, dried, and evaporated. The solid product (520 mg.) by recrystallisation from acetone–methanol gave cholest-6-en-3β-ol (V; R = H), m. p. 124—126°, $[\alpha]_D$ −88° ± 2° (*c*, 1·19) [Found (after drying at 65°/0·05 mm. for 3 hr.) : C, 80·3; H, 11·8. Calc. for $C_{27}H_{46}O,H_2O$: C, 80·1; H, 11·95%], giving a yellow colour with tetranitromethane–chloroform and a violet colour with acetic anhydride–sulphuric acid. The infra-red absorption spectrum of a Nujol mull showed bands at 3530—3200 and 1058 cm.$^{-1}$ (hydroxyl) and 1640, 770, 739, and 702 cm.$^{-1}$ [*cis*-CH=CH, consistent with a 6 : 7-double bond (cf. Henbest, Meakins, and Wood, *J.*, 1954, 800)]. Acetylation (acetic anhydride–pyridine at 100°) and recrystallisation of the product from methanol gave cholest-6-en-3β-yl acetate (V; R = Ac), m. p. 112—114°, $[\alpha]_D$ −93° ± 2° (*c*, 2·30) [Found (after drying at 20°/0·01 mm. for 18 hr.) : C, 81·4; H, 11·5. Calc. for $C_{29}H_{48}O_2$: C, 81·2; H, 11·3%], giving a violet colour in the Liebermann–Burchard test, and showing bands in the infra-red when examined in 2% carbon disulphide solution at 1734 and 1238 cm.$^{-1}$ (acetate) and 1634, 770, 739, and 702 cm.$^{-1}$ (*cis*-CH=CH : Δ^6). The benzoate (benzoyl chloride–pyridine at 20° for 18 hr.) had m. p. 132—133°, $[\alpha]_D$ −89°, −85° (*c*, 1·92, 1·0) [Found (after drying at 20°/0·01 mm. for 20 hr.) : C, 82·7; H, 10·2. Calc. for $C_{34}H_{50}O_2$: C, 83·2; H, 10·3%], after recrystallisation from methanol. The 3 : 5-*dinitrobenzoate* (3 : 5-dinitrobenzoyl chloride–benzene–pyridine at 20° for 18 hr.) had m. p. 188—190°, $[\alpha]_D$ −77° ± 2° (*c*, 1·27) [Found (after drying at 20°/0·01 mm. for 20 hr.) : C, 69·8; H, 8·2. $C_{34}H_{48}O_6N_2$ requires C, 70·2; H, 8·3%].

(b) *From 7α-bromo-6β-hydroxycholestan-3β-yl acetate* (I; R = Ac). The 7α-bromo-6β-hydroxy-acetate (45 mg.) was refluxed with activated zinc (400 mg.) (Fieser and Johnson, *J. Amer. Chem. Soc.*, 1940, 62, 576) in ethanol for 6 hr. The product (31 mg.), isolated in the usual way, by crystallisation from acetone gave cholest-6-en-3β-yl acetate (V; R = Ac), m. p. and mixed m. p. 112—114°. Hydrolysis of the acetate with 5% methanolic potassium hydroxide gave cholest-6-en-3β-ol, m. p. 124—126°, after recrystallisation from acetone–methanol.

(*c*) *From the 6α-analogue* (III; R = Ac). The 6α-compound acetate (45 mg.) on similar treatment with activated zinc in hot ethanol for 6 hr. gave cholest-6-en-3β-yl acetate (33 mg.), m. p. and mixed m. p. 112—114° after recrystallisation from acetone. The acetate (100 mg.), by treatment with lithium aluminium hydride (50 mg.) in ether at 20° for 18 hr. and subsequent working up, gave cholest-6-en-3β-ol, m. p. 122—124°, after recrystallisation from acetone–methanol.

6α : 7α-*Epoxycholestan-3β-yl Acetate.*—Cholest-6-en-3β-yl acetate (735 mg.) was treated with monoperphthalic acid (50 mg./c.c. : 2 mols.) in ethereal solution at 15° for 5 days (consumption : 1 mol. of peracid). Excess of peracid was destroyed with potassium iodide solution, and the ethereal solution washed with 0·1N-sodium thiosulphate. Working up in the usual manner yielded a crystalline solid (720 mg.). Recrystallisation from methanol gave 6α : 7α-*epoxycholestan-3β-yl acetate* (590 mg.) as needles, m. p. 179—180°, $[\alpha]_D$ −23° (*c*, 1·05) [Found (after drying at 60°/0·01 mm. for 2 hr.) : C, 78·2; H, 11·0. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%].

Reduction of 6α : 7α-*Epoxycholestan*-3β-*yl Acetate.*—6α : 7α-Epoxycholestan-3β-yl acetate (70 mg.) in dry ether (25 c.c.) was added to a solution of lithium aluminium hydride (40 mg.) in ether (20 c.c.). The solution was refluxed for ½ hr. and excess of the reagent decomposed with ice and 2N-sulphuric acid. Working up in the usual manner afforded cholestane-3β : 7α-diol, m. p. 151—152°, $[\alpha]_D$ +10° (*c*, 1·15), after crystallisation from methanol. Acetylation with acetic anhydride–pyridine at 15° gave the diacetate, m. p. 137—138°, $[\alpha]_D$ −16° (*c*, 1·12).

6β-*Bromo*-7α-*hydroxycholestan*-3β-*yl Acetate.*—6α : 7α-Epoxycholestan-3β-yl acetate (300 mg.) was dissolved in acetic acid (12 c.c.) cooled in ice water, and a 5% solution of hydrogen bromide in acetic acid (5 c.c.) added; after ½ hr. fine needles began to separate. Extraction with ether and the usual working up yielded 6β-*bromo*-7α-*hydroxycholestan*-3β-*yl acetate* (360 mg.), m. p. 149—150°, $[\alpha]_D$ −46·5° (*c*, 0·81), after crystallisation from ether–pentane [Found (after drying at 60°/0·01 mm. for 2 hr.): C, 66·2; H, 9·5; Br, 15·2. $C_{29}H_{49}O_3Br$ requires C, 66·25; H, 9·4; Br, 15·2%].

Hydrogenation of 6β-*Bromo*-7α-*hydroxycholestan*-3β-*yl Acetate.*—6β-Bromo-7α-hydroxycholestan-3β-yl acetate (75 mg.), potassium hydroxide (600 mg.), and 20% palladium–charcoal (50 mg.) in ethanol (25 c.c.) were shaken in hydrogen at 25° for 6 hr. The solution, by dilution and working up, gave cholestane-3β : 7α-diol, m. p. 152°, undepressed by admixture with the specimen obtained by lithium aluminium hydride reduction of 6α : 7α-epoxycholestan-3β-yl acetate.

Cholest-6-*en*-3β-*yl Acetate from the* 6β-*Bromo*-7α-*alcohol* (IX; R = Ac).—6β-Bromo-7α-hydroxycholestan-3β-yl acetate (45 mg.) was refluxed with activated zinc (450 mg.) in ethanol (12 c.c.) for 3 hr. The product (38 mg.), isolated in the usual way, on crystallisation from acetone gave cholest-6-en-3β-yl acetate, m. p. and mixed m. p. 112—113°.

One of us (D. R. J.) acknowledges a grant from the D.S.I.R., and another (R. W. R.) the financial support of Glaxo Laboratories Ltd. during 1952—53; we thank Glaxo Laboratories Ltd. for a gift of cholesterol, and for measuring the infra-red absorption spectra.

UNIVERSITY COLLEGE OF SWANSEA, UNIVERSITY OF WALES. [*Received, December 28th*, 1954.]

Steroids and Walden Inversion. Part XXIV. The Methylation of 3-Hydroxy-steroids.*

By J. R. LEWIS and C. W. SHOPPEE.

[Reprint Order No. 51001.]

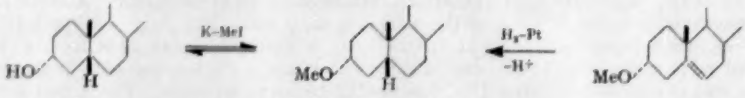
Methylation of coprostan-3α-ol with potassium–methyl iodide gives 3α-methoxycoprostane, identical with the product obtained from *epi*cholesteryl methyl ether by hydrogenation with platinum in the presence of hydrobromic, perchloric, or sulphuric acid. Similar methylation of coprostan-3β-ol does not cause inversion at $C_{(3)}$ and affords 3β-methoxycoprostane; partial epimerisation was observed only with a prolonged reaction time. In our hands, methylation of cholestan-3α-ol did not cause inversion at $C_{(3)}$ and furnished 3α-methoxycholestane in contrast to the observation by Beynon, Heilbron, and Spring (*J.*, 1937, 406).

DURING their investigation of the structure of *i*-cholesteryl methyl ether (6β-methoxy-3 : 5-*cyclo*cholestane), Beynon, Heilbron, and Spring (*J.*, 1937, 406; ref. *a*) found that methylation of either of the epimeric cholestan-3-ols with potassium and methyl iodide in boiling benzene gave 3β-methoxycholestane, previously prepared by Wagner-Jauregg and Werner (*Z. physiol. Chem.*, 1932, **213**, 119; ref. *b*). It seemed probable that epimerisation of the axial 3α-hydroxyl group to the more thermodynamically stable equatorial 3β-hydroxyl group under the influence of alkoxide ions had taken place before methylation in their experiments.

We have examined the methylation of the epimeric coprostan-3-ols in which the stereoelectronic relations are inverted as compared with the cholestan-3-ols. Methylation of coprostan-3α-ol (I; OH, equatorial) with potassium and methyl iodide in boiling benzene

* Part XXIII, *J.*, 1955, 694.

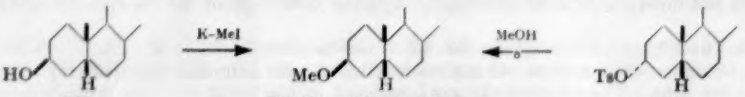
gave 3α-methoxycoprostane (II), identical with that obtained from *epi*cholesteryl methyl ether (III) by catalytic hydrogenation with platinum in the presence of hydrobromic, perchloric, or sulphuric acid (Lewis and Shoppee, *J.*, 1955, 1365, ref. *c*), and demethylated to coprostan-3α-ol (I).



(I) (II) M. p. 88°, [+36°] *e*; m. p. 88°, [+32°] (III)

Values in square brackets are $[\alpha]_D$.

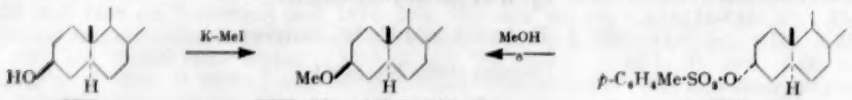
Coprostan-3β-ol (IV; HO, axial) by methylation under similar conditions gave 3β-methoxycoprostane (V), previously prepared by reductive methylation of coprostan-3-one (Babcock and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5472; ref. *d*) and by methanolysis of 3α-toluene-*p*-sulphonyloxycoprostane (VI) (Evans and Shoppee, *J.*, 1953, 540; ref. *e*).



(IV) (V) M. p. 63°, [+27°] *e*; m. p. 64/79°,* [+23°] *e*; m. p. 78°, [+28°] (VI)

* This designates double m. p.

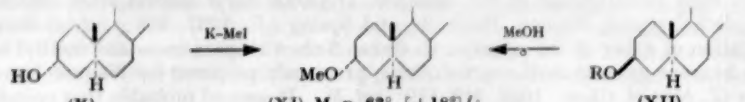
Since the expected inversion of coprostan-3β-ol (IV) to coprostan-3α-ol (I) did not occur, methylation of the epimeric cholestan-3-ols with potassium–methyl iodide was re-investigated. Cholestan-3β-ol (VII; OH, equatorial) gave 3β-methoxycholestane (VIII) recently obtained by methanolysis of 3α-toluene-*p*-sulphonyloxycholestane (IX) (Nace, *J. Amer. Chem. Soc.*, 1952, **74**, 5937; ref. *f*); contrary to the observation by Beynon, Heilbron, and Spring (*loc. cit.*), cholestan-3α-ol (X; OH, axial) gave 3α-methoxycholestane



(VII) (VIII) M. p. 81°, [+20°] *e*, *f*; m. p. 83°, [+20°] *b*, *f*; m. p. 83°, [+20°] (IX)

(XI), identical with the compound obtained by methanolysis of 3β-toluene-*p*-sulphonyloxycholestane (XII; R = *p*-$C_6H_4Me{\cdot}SO_2$) (Nace, *loc. cit.*), or of cholestan-3β-yl methyl sulphate (XII; R = $MeO{\cdot}SO_2$) (McKenna and Norymberski, *Chem. and Ind.*, 1954, 961; ref. *g*).

Attempts were made to repeat the conversion (X ⟶ VIII) observed by Beynon, Heilbron, and Spring. In view of the evidence adduced by Ashner and Doering (*J. Amer. Chem. Soc.*, 1949, **71**, 838) that the epimerisation of secondary alcohols involves an

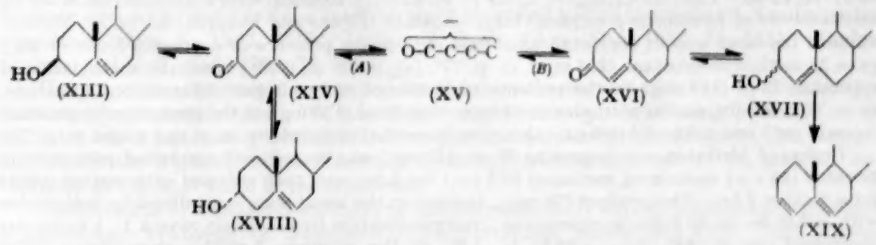


(X) (XI) M. p. 63°, [+18°] *f*; m. p. 64°, [+23°] *e*; m. p. 63°, [+21°] (XII)

oxidation–reduction analogous to that operating in Oppenauer oxidation and Meerwein–Ponndorf reduction, additions of (i) 5% of cholestan-3-one, (ii) methanol, and (iii) 5% of cholestan-3-one and methanol, to the methylations were made, but resulted in production only of the 3α-methyl ether (XI). Formation of the 3β-methyl ether (VIII) would have afforded a readily identifiable molecular compound, m. p. 74°. Similarly, coprostan-3β-ol

(IV), under the same conditions, gave only the 3β-methyl ether (V). Partial epimerisation of coprostan-3β-ol was obtained by extending the time of reaction with potassium in the presence of methanol from 1 to 3 hr.; reaction with methyl iodide then gave a product, m. p. 68°, $[\alpha]_D$ +29·5°, which appeared to be identical with a molecular compound artificially prepared from the two epimerides. Under similar conditions, cholestan-3α-ol (X) did not undergo epimerisation, but it is likely that prolonged reaction in the presence of alkoxide ions can cause some degree of epimerisation.

In connection with the mechanism of epimerisation suggested by Ashner and Doering, it is relevant that Heilbron, Barnett, Jones, and Verrill (*J.*, 1940, 1390) were able partially to convert cholesterol (XIII) and lumisterol [10α-ergosterol] into *epi*cholesterol (XVIII) and *epi*lumisterol, respectively, by treatment with aluminium *iso*propoxide in boiling xylene. The intermediate here must be the βγ-unsaturated ketone cholest-5-en-3-one (XIV); equilibrium with the corresponding αβ-unsaturated ketone cholest-4-en-3-one (XVI) is rapidly established in the presence of acidic or alkaline catalysts (Butenandt and



Schmidt-Thomé, *Ber.*, 1936, **69**, 882; Shoppee and Summers, *J.*, 1950, 687; Birch, *ibid.*, p. 2325; cf. Fieser and Stevenson, *J. Amer. Chem. Soc.*, 1954, **76**, 1728), and is greatly in favour of this. As has been pointed out by Birch, if protonation of the mesomeric anion (XV) is irreversible, then kinetic control (*A*) will lead to a high proportion of the unconjugated ketone (XIV), giving by reduction cholesterol and *epi*cholesterol; but if protonation of the mesomeric anion (XV) is reversible then thermodynamic control (*B*) will lead to the conjugated ketone (XVI), giving by reduction the epimeric cholest-4-en-3-ols (XVII) (Schoenheimer and Evans, *J. Amer. Chem. Soc.*, 1936, **58**, 182), which are readily dehydrated to cholesta-2 : 4-diene, which in turn is converted by heat into cholesta-3 : 5-diene (XIX). The 5% yield of *epi*cholesterol obtained by Heilbron, Barnett, Jones, and Verrill is thus due partly to the preferential production of cholesterol (XIII; OH, equatorial) and partly to thermodynamic as opposed to kinetic control of the equilibria in which the mesomeric anion (XV) is involved.

The infra-red absorption spectra of the methyl ethers (II, V, VIII, and XI) show that the C–OMe stretching vibration appears at slightly lower frequencies when the methoxyl group has the axial conformation [(V), $\nu_{max.}$ 1095 cm.$^{-1}$ in CS_2; (XI), $\nu_{max.}$ 1086 cm.$^{-1}$ in CS_2] than when it has the equatorial conformation [(II, VIII), $\nu_{max.}$ 1100 cm.$^{-1}$ in CS_2], which recalls the similar small difference in frequency observed between conformational pairs of 3-hydroxy-steroids by Cole, Jones, and Dobriner (*ibid.*, 1952, **74**, 5571). These infra-red spectra, *inter alia*, will be discussed in detail by Dr. J. E. Page in a forthcoming paper.

Experimental

For general details see *J.*, 1955, 694. Specific rotations were determined in $CHCl_3$; infra-red absorption spectra were measured in CS_2 on a Perkin–Elmer double-beam instrument.

3α-Methoxycoprostane from Coprostan-3-α-ol.—Coprostan-3α-ol (m. p. 116°; 850 mg.) was dissolved in benzene (40 c.c.), potassium (450 mg.) added, the solution heated to 70°, and the metal emulsified by vigorous agitation. After 1 hour's refluxing, methyl iodide (15 c.c.) was added and heating continued for 3 hr., potassium iodide being gradually precipitated. The solution was cooled to 0°, methanol added, and solvents removed in a vacuum. The residue was extracted with pentane, the pentane extracts were filtered through a column of aluminium

oxide, and the filtrate was evaporated to yield 3α-methoxycoprostane (470 mg.), m. p. 88°, $[\alpha]_D$ +32° (*c*, 1·3) [Found (after drying at 50°/0·01 mm. for 2 hr.): C, 83·6; H, 12·5%]. This gave no m. p. depression on admixture with a specimen prepared from *epi*cholesteryl methyl ether by hydrogenation with platinum in the presence of hydrobromic acid (Lewis and Shoppee, *J.*, 1955, 1365, and the infra-red absorption spectra were identical. Demethylation with hot 48% hydrobromic acid and acetic acid for 1·5 hr. (cf. Stoermer, *Ber.*, 1908, **41**, 323) gave an oil, which was chromatographed on aluminium oxide; after elution with pentane, use of benzene–pentane (1 : 9) gave an oil, which crystallised and proved to be 3α-methoxycoprostane, m. p. 86—88°. Elution with ether–benzene (1 : 9) gave crystalline material, which by recrystallisation from methanol furnished coprostan-3α-ol, m. p. and mixed m. p. 110—114°.

3β-Methoxycoprostane.—Coprostan-3β-ol (m. p. 100°; 1 g.) was heated with emulsified potassium (700 mg.) in benzene (50 c.c.) for 1 hr., methyl iodide (15 c.c.) was slowly added, and the mixture refluxed for 3 hr. The product was worked up as described above; elution from aluminium oxide with pentane gave 3β-methoxycoprostane (600 mg.), m. p. 78°, $[\alpha]_D$ +28·5° (*c*, 1·2), after crystallisation from acetone [Found (after drying at 50°/0·01 mm. for 2 hr.): C, 83·2; H, 12·45. Calc. for $C_{28}H_{50}O$: C, 83·5; H, 12·5%], identical with a specimen obtained by methanolysis of 3α-toluene-*p*-sulphonyloxycoprostane (Evans and Shoppee, *loc. cit.*). Methylation in the same way of coprostan-3β-ol (256 mg.) in the presence of coprostan-3-one (9 mg.) gave 3β-methoxycoprostane (244 mg.), m. p. 77°, $[\alpha]_D$ +28° (*c*, 0·75); similarly, methylation of coprostan-3β-ol (113 mg.) in the presence of methanol (0·5 c.c.) gave 3β-methoxycoprostane, m. p. 77°; finally, similar methylation of coprostan-3β-ol (173 mg.) in the presence of coprostan-3-one (5 mg.) and methanol (0·5 c.c.) also gave 3β-methoxycoprostane, m. p. and mixed m. p. 77°.

Prolonged Methylation.—Coprostan-3β-ol (123 mg.) was heated with emulsified potassium in benzene (25 c.c.) containing methanol (0·3 c.c.) for 3 hr., and then refluxed with methyl iodide for a further 3 hr. The product (78 mg.), isolated in the usual way, crystallised by inoculation with either 3α- or 3β-methoxycoprostane; recrystallisation from acetone gave a 1 : 1 molecular compound, m. p. 68°, $[\alpha]_D$ +29·5° (*c*, 2·3), of the epimeric 3-methoxycoprostanes. The molecular compound was also prepared by mixing equal quantities of the epimeric 3-methoxycoprostanes, and on crystallisation from acetone formed plates, m. p. 68°, undepressed on on admixture with either component.

3α-Methoxycholestane.—Cholestan-3α-ol (m. p. 183—185°; 1 g.) [prepared by the method of Marker, Kamm, and Whitmore (*J. Amer. Chem. Soc.*, 1935, **57**, 2358)], by methylation with methyl iodide after treatment with emulsified potassium in boiling benzene for 1 hr., yielded 3α-methoxycholestane (650 mg.), m. p. 63°, $[\alpha]_D$ +21° (*c*, 0·6), after crystallisation from acetone, and identical with a specimen prepared by methanolysis of 3β-toluene-*p*-sulphonyloxycholestane (Nace, *loc. cit.*). Methylation in the same way of cholestan-3α-ol (84 mg.) in the presence of cholestan-3-one (8 mg.) gave a product (77 mg.) which by crystallisation from acetone furnished 3α-methoxycholestane, m. p. and mixed m. p. 62—63°; similarly, methylation of cholestan-3α-ol (73 mg.) in the presence of methanol (0·3 c.c.) gave 3α-methoxycholestane (44 mg.), m. p. 63°; finally, similar methylation of cholestan-3α-ol (50 mg.) in the presence of cholestan-3-one (3 mg.) and methanol (0·2 c.c.) gave 3α-methoxycholestane (35 mg.), m. p. and mixed m. p. 62—63°. In each case, the methyl ether was isolated by elution from aluminium oxide with pentane.

Prolonged Methylation.—Cholestan-3α-ol (73 mg.) was heated with emulsified potassium in benzene (15 c.c.) containing methanol (0·3 c.c.) for 3·5 hr., and then refluxed with methyl iodide for a further 3 hr. The product (44 mg.), isolated in the usual way, crystallised from acetone in plates, m. p. 63°, undepressed by admixture with a sample of 3α-methoxycholestane.

Molecular Compound of 3α- and 3β-Methoxycholestane.—Equal quantities of the epimeric 3-methoxycholestanes were mixed and the mixture crystallised from acetone to give a molecular compound, m. p. 74°.

One of us (J. R. L.) acknowledges the financial support of the Department of Scientific and Industrial Research; we thank Glaxo Laboratories Ltd. for a gift of cholesterol and for the measurement of the infra-red absorption spectra.

University College of Swansea, University of Wales. [*Received, December 23rd*, 1954.]

Pteridine Derivatives. Part I. A New Synthesis of 2-Amino-4-hydroxypteridines.

By G. P. G. Dick and H. C. S. Wood.

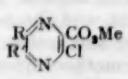
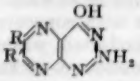
[Reprint Order No. 5928.]

A new method is reported for the synthesis of 2-amino-4-hydroxypteridines, namely, condensation of 2-chloro-3-methoxycarbonylpyrazines with guanidine salts.

Only two methods have been reported in the literature for the synthesis of pteridine derivatives from pyrazine intermediates. The first, due to Gabriel and Sohn (*Ber.*, 1907, **40**, 4857), consisted in the treatment of pyrazine-2 : 3-dicarboxyamide with potassium hypobromite to give 2 : 4-dihydroxypteridine in poor yield. In the second, Albert, Brown, and Cheeseman (*J.*, 1951, 474) synthesised 4-hydroxy- and 4-mercapto-pteridine by heating 2-aminopyrazine-3-carboxyamide and the 3-thiocarboxyamide with ethyl orthoformate and acetic anhydride, a reaction since extended to the synthesis of *N*-substituted pteridines (*idem*, *J.*, 1952, 4219; Taylor, *J. Amer. Chem. Soc.*, 1952, **74**, 1651; Taylor, Carbon, and Hoff, *ibid.*, 1953, **75**, 1904).

The pyrazinecarboxyamides required for these syntheses were obtained by degradation of more complex molecules. We now report a pteridine synthesis using pyrazine intermediates which are readily available from aliphatic compounds. In addition, this method will enable the 2-position in a 2-amino-4-hydroxypteridine molecule to be labelled isotopically at the final stage in the synthesis.

Condensation of 2-chloro-3-methoxycarbonylpyrazines (I) with guanidine salts provides a convenient synthesis of 2-amino-4-hydroxypteridine derivatives (II). The chloro-esters are prepared from the 2-hydroxypyrazine-3-carboxyamides (Jones, *ibid.*, 1949, **71**, 80), which are readily available by condensation of aminomalonamide with 1 : 2-dicarbonyl compounds.

(I)  (II) 

2-Hydroxypyrazine-3-carboxyamide was hydrolysed to the acid, the methyl ester of which with phosphorus oxychloride gave 2-chloro-3-methoxycarbonylpyrazine (I; R = R′ = H) in good yield. Condensation of the chloro-ester with guanidine was catalysed by sodium methoxide in boiling methanol or by potassium *tert.*-butoxide in boiling *tert.*-butyl alcohol, to give 2-amino-4-hydroxypteridine (II; R = R′ = H) in 20% yield. However, heating the chloro-ester and guanidine carbonate at 170° for 30 minutes gave an 89% yield. A similar fusion with urea did not give any 2 : 4-dihydroxypteridine.

The synthesis of 2-amino-4-hydroxy-6 : 7-diphenylpteridine (II; R = R′ = Ph) from the pyrazine (I; R = R′ = Ph) was carried out by fusion with guanidine; use of sodium methoxide, under the conditions used for the parent compound, gave none of the required pteridine, but good yields of 2-methoxy-5 : 6-diphenylpyrazine-3-carboxylic acid.

This new method could be applied to the synthesis of 2-amino-4-hydroxy-6-methylpteridine (II; R = Me, R′ = H), which is an intermediate in one of the most flexible methods for the synthesis of pteroylglutamic acid and its analogues (Boothe *et al.*, *ibid.*, 1948, **70**, 27. Roche Products Ltd., B.P. 624,394/1949). The starting material, 2-hydroxy-5-methylpyrazine-3-carboxyamide, has been obtained by the condensation of methyl glyoxal with aminomalonamide (Jones, *loc. cit.*). That this type of reaction gives only 3 : 5-disubstituted 2-hydroxypyrazines, and none of the isomeric 3 : 6-disubstituted compounds was confirmed by Spring and his co-workers (*J.*, 1949, 2707) who investigated the condensation of methylglyoxal and α-amino-hydroxamic acids.

In our hands, the condensation of methylglyoxal with aminomalonamide gave exclusively 2-hydroxy-6-methylpyrazine-3-carboxyamide. Aldehyde- and ketone-binding reagents (such as sodium hydrogen sulphite and hydrazine) which influence the orientation

when unsymmetrical dicarbonyl compounds are used in the synthesis of pteridines (Seeger, Cosulich, Smith, and Hultquist, *J. Amer. Chem. Soc.*, 1949, **71**, 1753; Forrest and Walker, *J.*, 1949, 2077) did not affect the orientation of our reaction. The use of sodium hydrogen sulphite facilitated the condensation however, and 2-hydroxy-6-methylpyrazine-3-carboxyamide was obtained in the absence of the usual basic catalyst.

Hydrolysis of the 6-methyl-amide gave 2-hydroxy-6-methylpyrazine-3-carboxylic acid which was converted into 2-chloro-3-methoxycarbonyl-6-methylpyrazine (I; R = H, R′ = Me) *via* the hydroxy-ester in the usual way. Fusion of the chloro-ester with guanidine carbonate gave 2-amino-4-hydroxy-7-methylpteridine (II; R = H, R′ = Me) in 80% yield.

The identity of the 2-amino-4-hydroxypteridines was confirmed in each instance by comparison of the infra-red spectrum with that of a specimen prepared by methods in the literature (cf. Mowat *et al.*, *ibid.*, 1948, **70**, 14; Cain, Mallette, and Taylor, *ibid.*, 1946, **68**, 1996; Forrest and Walker, *J.*, 1949, 83). The infra-red spectrum of 2-amino-4-hydroxy-7-methylpteridine (II; R = H, R′ = Me) was different from that of the 6-methyl isomer (II; R = Me, R′ = H) (*idem, ibid.*, p. 2080).

Experimental

Yields of substances that have no definite m. p. refer to the stage when they appeared homogeneous in paper chromatography in butanol–5N-acetic acid (7 : 3) on being viewed in ultra-violet light of wave-lengths **254** and **365** mμ.

Aminomalonamide.—Ethyl aminomalonate, the precursor of aminomalonamide, is best prepared on a large scale by the catalytic reduction of ethyl (hydroxyimino)malonate (Schipper and Day, *J. Amer. Chem. Soc.*, 1952, **74**, 350). It is readily converted into aminomalonamide by treatment with alcoholic ammonia (Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 80).

2-Hydroxy-6-methylpyrazine-3-carboxyamide.—(*a*) Freshly prepared methylglyoxal (Riley, Morley, and Friend, *J.*, 1932, 1875) was treated with aminomalonamide as described by Jones (*loc. cit.*). The yellow sodium salt which separated was collected after 2 days at 0°, washed with a small volume of water, and suspended in moist acetone (250 c.c.). The mixture was adjusted to pH 4 with concentrated hydrochloric acid, and the buff solid (13·0 g., 70%) which separated was collected, washed with ice-cold water and acetone, and dried. Rigorous chromatographic examination of the product, and the mother-liquors, did not reveal any fluorescent material other than the solid isolated. Recrystallization from methanol (charcoal) gave *2-hydroxy-6-methylpyrazine-3-carboxyamide* as pale yellow needles, m. p. 219—220° (decomp.) (Found: C, 46·9; H, 4·7; N, 28·0. $C_6H_7O_2N_3$ requires C, 47·1; H, 4·6; N, 27·5%).

(*b*) Freshly prepared methylglyoxal (12 g.) in water (30 c.c.) was treated with sodium hydrogen sulphite (10 g.), and the mixture set aside at room temperature for 30 min. Finely powdered aminomalonamide (20 g.) was added, and the mixture was heated on a water-bath until the solid had dissolved. Refrigeration gave a semi-solid buff mass which was purified *via* the sodium salt as before [yield 70%; m. p. 219—220° (decomp.)].

2-Hydroxypyrazine-3-carboxylic Acids.—(*a*) 2-Hydroxypyrazine-3-carboxyamide (1·0 g.) (Jones, *loc. cit.*) and sodium hydroxide (1·0 g.) in ethanol (30 c.c.) were heated in a steel bomb at 170° for 6 hr. After cooling, the ethanol was evaporated, the residue dissolved in aqueous sodium hydrogen carbonate, and the solution treated with charcoal and filtered. The filtrate was acidified with concentrated hydrochloric acid to pH 4 and allowed to cool. The solid was collected, washed with ice-cold water, and dried at 100° (0·61 g., 60%). The m. p. was 218—219° (decomp.), undepressed when mixed with a specimen prepared from 2-aminopyrazine-3-carboxylic acid (Spoerri and Fibel, *ibid.*, 1948, **70**, 3908).

(*b*) Similar hydrolysis of the diphenyl-amide gave *2-hydroxy-5 : 6-diphenylpyrazine-3-carboxylic acid* (91%) as golden needles (from aqueous acetone), m. p. 216—217° (decomp.) (Found: C, 69·7; H, 3·9; N, 9·4. $C_{17}H_{12}O_3N_2$ requires C, 69·8; H, 4·1; N, 9·6%)

(*c*) The sodium salt of 2-hydroxy-6-methylpyrazine-3-carboxyamide (3·0 g.) was dissolved in 5N-sodium hydroxide (20 c.c.), and the solution was refluxed until evolution of ammonia had ceased (30 hr.). The solution was stirred and treated with concentrated hydrochloric acid until the pH was 7—8, then some silica was filtered off. The filtrate was taken to pH 4—5, treated with charcoal, and concentrated *in vacuo* to 10 c.c. in an atmosphere of nitrogen. The dark violet solution deposited needles on cooling (1·3 g., 50%). Crystallization from methanol containing a few drops of water gave 2-hydroxy-6-methylpyrazine-3-carboxylic acid as thick clear needles which became opaque on drying, m. p. 188—189° (decomp.) (Found: C, 47·0;

H, 4·0; N, 18·3. Calc. for $C_8H_6O_2N_2$: C, 46·8; H, 3·9; N, 18·2%), recorded by Jones (*loc. cit.*) as a tan powder, m. p. 183—184°.

2-Hydroxy-3-methoxycarbonylpyrazines.—(*a*) 2-Hydroxy-5 : 6-diphenylpyrazine-3-carboxylic acid (7·5 g.) in dry boiling methanol (300 c.c.) was treated with dry hydrogen chloride until it had completely dissolved (about 20 min.), and the solution was refluxed for a further 2 hr. When the reaction mixture was cooled, *2-hydroxy-3-methoxycarbonyl-5 : 6-diphenylpyrazine* was deposited as yellow needles. These were collected, and the mother-liquors concentrated to *ca.* 50 c.c. *in vacuo*, a second crop being obtained. Recrystallization from methanol gave the hydroxy-ester as fine yellow needles (6·65 g., 89%), m. p. 204—205° (Found : C, 70·7; H, 4·7; N, 8·9. $C_{18}H_{14}O_3N_2$ requires C, 70·6; H, 4·6; N, 9·1%).

(*b*) 2-Hydroxy-6-methylpyrazine-3-carboxylic acid was esterified as above, to give the *methyl ester* (100%) as clear needles (from methanol); m. p. 174—175° (decomp.) (Found : C, 49·8; H, 4·7; N, 16·6. $C_7H_8O_3N_2$ requires C, 50·0; H, 4·8; N, 16·7%).

2-Chloro-3-methoxycarbonylpyrazines.—(*a*) 2-Hydroxy-3-methoxycarbonylpyrazine was converted into the chloro-ester by treatment with phosphorus oxychloride. [This preparation was first carried out in the Department of Medical Chemistry, the Australian National University; Albert, Brown, and Wood, unpublished work.]

(*b*) 2-Hydroxy-3-methoxycarbonyl-5 : 6-diphenylpyrazine (3·5 g.) and redistilled phosphorus oxychloride (23 c.c.) containing one drop of concentrated sulphuric acid were mixed in a Carius tube. The mixture was heated at 110° (bath) for 10 min.; evolution of hydrogen chloride had then ceased. The tube was then sealed and heated at 160° for 5·5 hr. The dark yellow solution was poured on cracked ice (200 g.), and stirred for 30 min., during which a buff solid separated. This was collected, washed with water, and recrystallised from methanol, to give small plates of *2-chloro-3-methoxycarbonyl-5 : 6-diphenylpyrazine* (3·0 g., 81%), m. p. 113—114°. Recrystallization from methanol–light petroleum (b. p. 60—80°) followed by sublimation gave a sample of m. p. 116—116·5° (Found : C, 66·6; H, 4·0; N, 8·9; Cl, 11·5. $C_{18}H_{13}O_2N_2Cl$ requires C, 66·6; H, 4·0; N, 8·6; Cl, 10·9%).

The yield at 150° was only 50%, and at 190° 14%. The use of a mixture of phosphorus oxychloride and diethylaniline (cf. Kenner, Lythgoe, Todd, and Topham, *J.*, 1943, 574), or of phosphorus oxychloride and phosphorus pentachloride (Karmas and Spoerri, *J. Amer. Chem. Soc.*, 1952, **74**, 1580), was unsuccessful.

(*c*) 2-Hydroxy-3-methoxycarbonyl-6-methylpyrazine (0·3 g.) was refluxed with redistilled phosphorus oxychloride (6 c.c.) containing one drop of concentrated sulphuric acid for 5 hr. The mixture was poured on cracked ice (100 g.) and stirred for 30 min. Ethyl acetate (30 c.c.) was added to the ice-cold solution, and the pH was adjusted to 8 with concentrated aqueous ammonia. The aqueous layer was saturated with sodium chloride and was extracted with ethyl acetate for 24 hr. The extract was dried and evaporated to dryness *in vacuo* to give a brown gum. Crystallisation from methanol (charcoal) gave *2-chloro-3-methoxycarbonyl-6-methylpyrazine* (0·2 g., 61%) as small yellow needles, m. p. 82—83°. Recrystallization from light petroleum (b. p. 60—80°) gave plates, m. p. 84—85° (Found : C, 45·7; H, 3·4. $C_7H_7O_2N_2Cl$ requires C, 45·1; H, 3·8%).

2-Amino-4-hydroxypteridine.—(*a*) 2-Chloro-3-methoxycarbonylpyrazine (1·0 g.), finely powdered and mixed with guanidine carbonate (2·0 g.), was heated at 170° (bath) for 30 min., with occasional stirring; effervescence took place, and the mixture became brown. On cooling, the residual solid was dissolved in boiling water (50 c.c.), and the solution was filtered. After treatment with charcoal, and filtration, the boiling solution was brought to pH 5 with 3N-hydrochloric acid. The pale yellow solid which separated, was collected at 90—100°, washed with boiling water (25 c.c.) and ethanol (15 c.c.), and dried at 100° to give 2-amino-4-hydroxypteridine (0·84 g., 89%), m. p. > 360°.

A sample (0·37 g.) was dissolved in hot 2N-sodium hydroxide (1·8 c.c.), the solution filtered hot, and 10N-sodium hydroxide (1·8 c.c.) added to the filtrate. The yellow sodium salt, which separated on cooling, was collected, washed with 2·5N-sodium hydroxide, and air-dried to give fine yellow needles. These were dissolved in boiling water (9 c.c.), and the hot solution was poured slowly into boiling 3N-acetic acid (30 c.c.). The pale yellow solid which separated was collected, washed as before, and dried at 135° (Found : C, 43·9; H, 3·0; N, 42·6. Calc. for $C_6H_5ON_5$: C, 44·2; H, 3·1; N, 42·9%).

(*b*) Guanidine hydrochloride (1·11 g.) was added to a solution of sodium (1·06 g.) in dry methanol (40 c.c.). The solution was filtered from sodium chloride, and 2-chloro-3-methoxycarbonylpyrazine (2·0 g.) was added. A clear, bright scarlet solution resulted on shaking, and this was refluxed for 30 hr., during which further precipitation of sodium chloride took place.

The filtered solution was diluted with water (60 c.c.), and the pH of the boiling solution was adjusted to 4·5 with warm glacial acetic acid. The yellow bulky precipitate (0·375 g., 20%) was collected and purified as above. The yield fell when the reaction was carried out at higher temperatures in a sealed tube, or when the period of refluxing was reduced.

2-Amino-4-hydroxy-6 : 7-diphenylpteridine.—2-Chloro-3-methoxycarbonyl-5 : 6-diphenylpyrazine (0·2 g.) was fused with guanidine carbonate (0·4 g.) as before. The mixture was extracted with boiling water to leave an orange solid (0·230 g.). This was purified by dissolution in hot 2N-sodium hydroxide (20 c.c.), filtration, and pouring of the warm filtrate into boiling glacial acetic acid (10 c.c.). The yellow solid which separated was collected at 90—100°, washed with warm water, and ethanol, and dried to give 2-amino-4-hydroxy-6 : 7-diphenylpteridine (0·13 g., 70%), m. p. > 360°. Recrystallization from dimethylformamide gave a yellow microcrystalline solid which was dried at 135° (Found : C, 68·3; H, 4·0; N, 22·4. Calc. for $C_{18}H_{12}ON_4$: C, 68·6; H, 4·2; N, 22·2%).

2-Amino-4-hydroxy-7-methylpteridine.—2-Chloro-3-methoxycarbonyl-6-methylpyrazine (0·135 g.) was fused with guanidine carbonate (0·4 g.) as before. The product was isolated as in the case of the unsubstituted compound to give 2-amino-4-hydroxy-7-methylpteridine (0·105 g., 80%), m. p. > 360°. This was purified *via* the sodium salt and dried at 135° (Found : C, 44·9; H, 4·2. Calc. for $C_7H_7ON_4,0·5H_2O$: C, 45·2; H, 4·3%).

Authentic material was prepared from 2 : 4 : 5-triamino-6-hydroxypyrimidine (Forrest and Walker, *J.*, 1949, 83), and dried at 135° (Found : C, 45·0; H, 4·3%).

2-Methoxy-5 : 6-diphenylpyrazine-3-carboxylic Acid.—To a solution of sodium (0·06 g.) in dry methanol (7 c.c.) were added guanidine hydrochloride (0·06 g.) and 2-chloro-3-methoxycarbonyl-5 : 6-diphenylpyrazine (0·2 g.). The mixture was refluxed for 12 hr., during which a white bulky precipitate separated. This was collected and dissolved in boiling water, and the filtrate was brought to pH 4 with glacial acetic acid. Crystallization occurred on cooling, to give fluffy white needles (0·096 g.), m. p. 179° (decomp.). The filtrate from the reaction mixture was concentrated *in vacuo*, warm water was added to dissolve any solid material, and the solution was filtered from traces of slime. The clear filtrate was adjusted to pH 4 with glacial acetic acid, and, on cooling, a further deposit of crystals was formed (0·04 g.), m. p. 175° (decomp.) (total yield 73%). Recrystallization from aqueous methanol gave *2-methoxy-5 : 6-diphenylpyrazine-3-carboxylic acid* as small white needles, m. p. 180—181° (decomp.) (Found : C, 70·7; H, 4·3; N, 8·9. $C_{18}H_{14}O_3N_2$ requires C, 70·6; H, 4·6; N, 9·2%). Care must be taken during the preparation of this material that it does not become mixed with its sodium salt which crystallizes readily from water as white plates, m. p. 254—256° (decomp.). The same methoxy-acid, m. p. and mixed m. p. 178—180° (decomp.), is obtained from 2-chloro-3-methoxycarbonyl-5 : 6-diphenylpyrazine and sodium methoxide in the absence of guanidine.

The methoxy-acid (0·2 g.) was esterified with methanol and dry hydrogen chloride, by the method employed for the esterification of the corresponding hydroxy-acid. *2-Methoxy-3-methoxycarbonyl-5 : 6-diphenylpyrazine* (0·2 g., 95%) recrystallized from methanol as fluffy white needles, m. p. 118·5—119° (Found : C, 71·2; H, 5·0; N, 8·6. $C_{19}H_{16}O_3N_2$ requires C, 71·2; H, 5·0; N, 8·8%).

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THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, November 30th*, 1954.]

The Electric Moment of 1-Methylpyrrolid-2-one.

By ERNST FISCHER.

[Reprint Order No. 5677].

IN a recent paper (*J.*, 1952, 4525; 1953, 2836) a comparison was made between calculated and "experimental" dipole moments of pyrrolid-2-one, and conclusions were drawn regarding the contribution of dipolar mesomers to the structure of this compound. At that time no reliable data were available for the dipole moment of this ketone, and the value for piperid-2-one was used instead. The moments of pyrrolid-2-one and its 1-methyl derivative have now been measured, the results corroborating the conclusions reached in the previous paper.

Pyrrolid-2-one, like oxazolid-2-one described previously, is strongly associated in benzene solution, as shown by the fact that the slope of the curve of dielectric increment against concentration increases with decreasing concentration even at weight fractions below 10^{-3}. With the methylated compound, on the other hand, this curve is rectilinear up to weight fractions above 8×10^{-3}, proving that the *N*-hydrogen atom is responsible for the association. From the tangent of the plot of dielectric increment against weight fractions up to 10^{-3} the moment calculated for pyrrolid-2-one is 3·7 D. Because of the pronounced association this value is probably still too low, and is mentioned here only because the value of 2·3 D reported by Devoto (*Gazzetta*, 1933, **63**, 495) appears to be much too low as it is based on measurements at much higher concentrations, where association is of course considerable. For 1-methylpyrrolid-2-one the moment found was 4·09 ± 0·04 D, to be compared with 4·0 D observed for 1-methylpiperidone. Comparison with the calculated moment of 2·8 D leads to a contribution by dipolar mesomers of about 16%, thus corroborating earlier results with open amides (Kumler, *J. Amer. Chem. Soc.*, 1952, **74**, 261).

Experimental.—Pyrrolid-2-one and 1-methylpyrrolid-2-one were kindly given by Messrs. General Aniline and Film Corporation, New York, and purified by vacuum distillation immediately before use. Pyrrolid-2-one had n_D^{25} 1·486, d_4^{25} 1·107; 1-methylpyrrolid-2-one had n_D^{25} 1·469, d_4^{25} 1·027. The resulting molar refractions R_D for the sodium-*D* line are 22·0 and 26·9 ml., in good agreement with the values calculated from bond refractions (Vogel *et al.*, *J.*, 1952, 514).

The dipole moment was calculated from the slopes of the rectilinear plots of dielectric constant increment $\Delta\varepsilon(= \varepsilon_{sol.} - \varepsilon_{solv.})$ and density increment $\Delta d(= d_{sol.} - d_{solv.})$ against weight fraction w in benzene at 30° (cf. Bergmann, Weizmann, and Fischer, *J. Amer. Chem. Soc.*, 1950, **72**, 5009, where the symbols and the method of extrapolation used are explained). Experimental figures for 1-methylpyrrolid-2-one are given in the Table.

10^5w	27	45·5	63·5	81·5	109	145	172·5	1783
$10^4\Delta\varepsilon$	49	82	115	148	197	262	310	—
$10^3\Delta d$	—	—	—	—	—	—	—	291

$C\alpha\varepsilon_0 = 3{\cdot}415$, $\beta = 0{\cdot}188$, $P_\infty = 366$ ml., $1{\cdot}05R_D = 28$ ml., $P_\infty - 1{\cdot}05R_D = 338$ ml., $\mu = 4{\cdot}09 \pm 0{\cdot}04$ D.

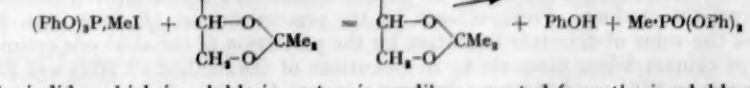
WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL. [*Received, August 23rd*, 1954.]

The Preparation of Glycerol Iodides.

By T. H. BEVAN, T. MALKIN, and D. B. SMITH.

[Reprint Order No. 5866.]

GLYCEROL α-IODIDE [glycerol α-iodohydrin], a starting material for the preparation of diglycerides (Fischer, *Ber.*, 1920, **53**, 1621) and phosphatidic acids (Hessel, Morton, Todd, and Verkade, *Rec. Trav. chim.*, 1954, **73**, 150), is prepared by replacement of chlorine in 2 : 3-*iso*propylidenedioxypropyl chloride (Fischer and Pfähler, *Ber.*, 1920, **53**, 1606), or of the toluene-*p*-sulphonyl group in 2 : 3-*iso*propylidenedioxypropyl toluene-*p*-sulphonate (Fischer and Baer, *J. Amer. Chem. Soc.*, 1948, **70**, 609) by heating in a sealed tube with sodium iodide in acetone, followed by hydrolysis of the resulting *iso*propylidene iodide. In order to avoid the use of sealed tubes, we used the new method for preparing iodides described by Landauer and Rydon (*J.*, 1953, 2224), and we find that yields of 75% are readily obtained as follows :



The iodide, which is soluble in water, is readily separated from the insoluble diphenyl methylphosphonate.

Similarly, 1 : 3-benzylideneglycerol gives glycerol β-iodide in 56% yield. Glattfield and Klaas (*J. Amer. Chem. Soc.*, 1933, **55**, 1114) obtained an 18% yield by heating glycerol β-chloride with sodium iodide in acetone under pressure.

Experimental.—Glycerol α-iodide. Under anhydrous conditions, 1 : 2-*O*-*iso*propylideneglycerol (35 g., 0·26 mole) (Malkin and Shurbagy, *J.*, 1936, 1634) was added to triphenyl phosphite methiodide (90 g., 0·22 mole), and the temperature was kept below 50°. After 6 hr., the brown viscous oil was freed from phenol and iodine, by vigorous shaking with 5% sodium hydrate solution, followed by washing with water. 5N-Sulphuric acid (5 ml.) in 86% ethanol (125 ml.) was added to the well-drained oil, and after 20 hr. hydrolysis was completed by 5 minutes' refluxing. The cold solution was neutralised with barium carbonate, filtered, and evaporated on the water-bath under reduced pressure to an oil, from which the iodohydrin was extracted by several washings with water. After the addition of common salt to the combined washings, the iodide was extracted with ether, the ether solution was dried (Na_2SO_4), and the ether was distilled off. The residual oil, crystallised from chloroform and then from chloroform–light petroleum (b. p. 40—60°), yielded colourless platelets (29·2 g.), m. p. 48·5—49·5°.

If the intermediate *iso*propylidene iodide is required the initial reaction product is taken up in ether, freed from phenol and iodine, and dried. After removal of ether, the product is distilled. 2 : 3-*iso*Propylidenedioxypropyl iodide boils at 70—72°/2 mm. The by-product, diphenyl methylphosphonate, boils 85—90° higher.

Glycerol β-iodide. Triphenyl phosphite (24·3 g., 0·079 mole) and methyl iodide (15 g., 0·12 mole) were refluxed under anhydrous conditions for 36 hr. After cooling, the still warm liquid was washed several times with anhydrous ether, which was decanted and, whilst the phosphite methiodide was still liquid 1 : 3-*O*-benzylideneglycerol (12 g., 0·067 mole) (Verkade and van Roon, *Rec. Trav. chim.*, 1942, **61**, 831) was added, the temperature being kept below 50°. After 8 hr. the dark brown liquid was washed several times with sodium hydroxide solution and taken up in ether for further washing with alkali and water. The ether was removed, and the residual oil was hydrolysed by 5N-sulphuric acid (3 ml.) in 85% ethanol (75 ml.) at 40° for 30 hr. The procedure from this point is as described for the α-iodide, yielding white platelets (7 g.) m. p. 53° (Glattfield and Klaas, *loc. cit.*, found m. p. 53°) (Found : I, 63·3. Calc. for $C_3H_7O_3I$: I, 62·9%). The slight difference in technique from the previous preparation is due to the fact that 1 : 3-*O*-benzylideneglycerol is a solid, whereas 1 : 2-*O*-*iso*propylideneglycerol is a liquid.

THE UNIVERSITY, BRISTOL, 8. [*Received, November 10th*, 1954.]

The Preparation of the Mononitrocinnamaldehydes.

By W. DAVEY and J. R. GWILT.

[Reprint Order No. 5881.]

MONONITROCINNAMALDEHYDES have been prepared by alkali-catalysed condensation of acetaldehyde with the appropriate nitrobenzaldehyde in aqueous-alcohol (Kinkelin, *Ber.*, 1885, **18**, 483) or in solution in the acetaldehyde itself (Baeyer and Drewsen, *Ber.*, 1883, **16**, 2205; Kinkelin, *loc. cit.*; Göhring, *Ber.*, 1885, **18**, 371, 719). Nitration of cinnamaldehyde in sulphuric acid with potassium nitrate (Diehl and Einhorn, *ibid.*, p. 2335; Mohlau and Adam, *Z. Farbst. Industr.*, 1906, **5**, 402) gave *o*- and *p*-nitrocinnamaldehydes whilst nitration in acetic anhydride (Mills and Evans, *J.*, 1920, **117**, 1037) gave *o*-nitrocinnamaldehyde in 36% yield. The results of condensation and nitration are discussed below under the individual aldehydes.

By a method substantially that of Baeyer and Drewsen (*loc. cit.*) a 61% yield of *o*-nitrocinnamaldehyde was obtained, in agreement with the findings (70% yield) of Diehl and Einhorn (*loc. cit.*). Kinkelin's method (*loc. cit.*) gave no more than 26% though Diehl and Einhorn (*loc. cit.*) reported 40%. In both condensations a gum proved difficult to remove from the product. Previous work by the present authors (*J.*, 1950, **204**, 3348) had shown the value of diacetate formation for the protection of the aldehyde group and nitration of cinnamylidene diacetate by modifications of the method of Mills and Evans (*loc. cit.*) gave an 85% yield of *o*-nitrocinnamaldehyde. Diacetate formation has usually been achieved by use of sulphuric acid as catalyst but not more than 50% of cinnamylidene diacetate was thus obtained; the diacetate was however obtained in 95% yield by the use of orthophosphoric acid and could be used *in situ* for nitration. The dilute hydrochloric acid added to the final reaction mixture in the method of Mills and Evans (*loc. cit.*)

hydrolysed the *o*-nitrocinnamylidene diacetate; the observed rise in temperature is not due solely to the reaction between acetic anhydride and water under these conditions.

Kinkelin (*loc. cit.*) reported that Baeyer and Drewsen's method (*loc. cit.*) gave poor yields of *m*-nitrocinnamaldehyde whilst Göhring (*loc. cit.*) claimed almost quantitative yields. In the present work yields of only 32% were obtained by Baeyer and Drewsen's method, but the alternative method developed by Kinkelin and claimed by him to give a 50% yield was found to give a 61% yield and the product was readily purified, though some evidence of further condensation was obtained. Variations in the method, or use of alternative methods, in general gave lower yields.

p-Nitrocinnamaldehyde proved the most difficult isomer to obtain pure. Yields of 38% and 48% were obtained by the methods of Göhring (*loc. cit.*) and of Kinkelin (*loc. cit.*) respectively. Waley (*J.*, 1948, 2010) has reported yields of 72% by a modification of Göhring's method and his method appears to be the most satisfactory though the experimental conditions are apparently somewhat critical. Attempts to prepare the aldehyde by direct nitration did not lead to a practicable method and increasing severity in nitration conditions gave oxidation to *p*-nitrobenzaldehyde and then to *p*-nitrobenzoic acid. Dilution of the reagents before reaction, *e.g.*, with acetic acid, prevented nitration, unchanged cinnamaldehyde being recovered.

o-Nitrocinnamaldehyde has been readily converted by reduction into quinoline in 82% yield and this represents a convenient preparative method.

Experimental

Preparation of Diacetates.—Acetic anhydride (500 ml.) and orthophosphoric acid (5 ml.; *d* 1·75) were mixed at 20° and the aldehyde (1 mole) added during 5—10 min. with stirring. After a further 30 minutes' stirring, during which the temperature rose only to *ca.* 30°, the mixture was poured into a large excess of water, and the product isolated and purified. By this method cinnamylidene and *o*-, *m*-, and *p*-nitrobenzylidene diacetate were obtained in 95—97% yield and ethylidene diacetate in 90% yield.

Nitration of Cinnamylidene Diacetate.—Cinnamaldehyde (105 g.) was dissolved in acetic anhydride (500 ml.), and phosphoric acid (5 ml.; *d* 1·75) was added with cooling and stirring. After 1 hr., the solution was held at −5° to 0° by the addition of solid carbon dioxide whilst nitric acid (35 ml.; *d* 1·52) was added during 30 min. The solution was then allowed to reach room temperature during 2 hr. with stirring and poured into ice-water (4 l.). Hydrochloric acid (250 ml.; *d* 1·16) was added during 15 min. and the mixture left overnight. The product consisted of a mixture of *o*-nitrocinnamaldehyde and *o*-nitrocinnamylidene diacetate. It was dissolved in ethanol (600 ml.), sulphuric acid [40 ml. (*d* 1·84) + 400 ml. of water] was added, and the whole refluxed for 2 hr. On cooling, *o*-nitrocinnamaldehyde separated as sandy needles and dilution with water gave a further crop. The total yield was recrystallised twice from ethanol (charcoal), to give pale yellow needles of *o*-nitrocinnamaldehyde (103 g., 84%), m. p. and mixed m. p. 128°. Alternatively the mixture of aldehyde and diacetate was hydrolysed by 2 hours' refluxing with 5N-hydrochloric acid (500 ml.) or 1·5 hours' with magnesium hydroxide suspension (40 g. in 500 ml. of water).

Reduction of o-*Nitrocinnamaldehyde.*—*o*-Nitrocinnamaldehyde (10 g.), water (250 ml.), ferrous sulphate heptahydrate (150 g.), and hydrochloric acid (1 ml.; *d* 1·18) were together heated to 90° under reflux. Ammonia solution (*d* 0·88) was added through the condenser at two-minute intervals in portions of 25, 10, 10, and 10 ml., with vigorous shaking after each addition. The mixture was held at 90° for 1 hr. and then steam-distilled. The distillate was extracted with ether, the extract washed with a little water, and dried (Na_2SO_4) and the ether was removed. The residual liquid was distilled, to yield quinoline (6·0 g., 82%), b. p. 123—128°/18 mm. (tartrate, m. p. 126°; picrate, m. p. 203°).

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The Preparation of 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*Octahydrodibenzothiophen.*

By W. Cooper.

[Reprint Order No. 5884.]

1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-Octahydrodibenzothiophen has been synthesised by Cagniant and Cagniant (*Bull. Soc. chim., France*, 1952, **326**) from 1 : 2 : 3 : 4-tetrahydrothionaphthen. The intermediates in this synthesis are not readily available, but it has now been found that this octahydro-compound can be prepared conveniently by direct reaction of sulphur with *cyclo*hexanone or 2-*cyclo*hex-1′-enyl*cyclo*hexanone. The latter is probably an intermediate in the formation of the dibenzothiophen from *cyclo*hexanone.

Experimental.—1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-*Octahydrodibenzothiophen.* (*a*) From *cyclo*hexanone. Sulphur (32 g.) and *cyclo*hexanone (200 g.) were heated under reflux (nitrogen atmosphere; in air some oxidation occurred to give adipic acid) for 20 hr.; hydrogen sulphide was steadily evolved. After cooling, unchanged sulphur (16 g.) was removed, and dissolved sulphur, polysulphides, and thiols were extracted with aqueous sodium hydroxide. Fractionation of the neutral layer gave: (i) *cyclo*hexanone (110 g.); (ii) 2-*cyclo*hex-1′-enyl*cyclo*hexanone (9 g.), b. p. 152—154°/18 mm., n_D^{20} 1·5117, d_{20}^{20} 1·026 (oxime, m. p. 148°) [Found: O in CO (by reaction with hydroxylamine hydrochloride and titration of the acid liberated), 8·8. Calc. for $C_{12}H_{18}O$: O in CO, 9·0%] (infra-red spectrum identical with that of a sample prepared by Rapson's method, *J.*, 1941, 15); (iii) 1 : 2 : 3 : 4 : 6 : 7 : 8 : 9-octahydrodibenzothiophen (20 g.), m. p. 32° after recrystallisation from alcohol (Cagniant and Cagniant, *loc. cit.*, report m. p. 31°), b. p. 120°/1 mm., n_D^{20} 1·5702 {Found: C, 74·4; H, 8·2; S, 17·0%; *M* (ebullioscopic in benzene), 195; $[R]_D$, 59·0. Calc. for $C_{12}H_{16}S$: 3, 74·9; H, 8·4; S, 16·7%; *M*, 192·2; $[R]_D$, 58·8}, light absorption (by Mr. C. E. Kendall), max. at 2400 Å (ε 7560); and (iv) a high-boiling viscous residue (12 g.) containing much combined sulphur and not examined in detail.

The infra-red spectrum of the octahydrodibenzothiophen has been deposited with the Society (C.S. No. 175) * by Mr. W. H. T. Davison.

Heating the octahydrodibenzothiophen (1 g.) with selenium (3 g.) at 360° for 4 hr. gave a crystalline sublimate (0·6 g.) of dibenzothiophen, m. p. 97° (picrate, m. p. 123°), the ultra-violet spectrum of which was identical with that given by Sawicki and Ray (*J. Amer. Chem. Soc.*, 1952, **74**, 4120).

(*b*) From 2-*cyclo*hex-1′-enyl*cyclo*hexanone. Sulphur (8 g.) and this ketone (30 g.) were heated for 10 hr. at 170°. Water and hydrogen sulphide were formed. The red-brown product, when washed with alkali and fractionated, gave unchanged ketone (5 g.), the octahydrodibenzothiophen (16 g., 45%), and a high-boiling residue.

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Chemical Research Division, Dunlop Research Centre, Birmingham. [*Received, November 16th*, 1954.]

Thermodynamic Indicator Constants of Dinitrophenols in Dioxan–Water Mixtures.

By S. Kertes.

[Reprint Order No. 5894.]

For the measurements and calculation of the thermodynamic indicator constants Kolthoff and Guss's method (*J. Amer. Chem. Soc.*, 1938, **60**, 2516) was used. Judson and Kilpatrick (*ibid.*, 1949, **71**, 3110) used a similar method for determination of ionization constants for 2 : 5-dinitrophenol in aqueous solution. Although there is an extensive literature on nitrophenols in aqueous solution, there is little on the behaviour of those indicator acids in non-aqueous media (Eisenbrand and Halban, *Z. phys. Chem.*, 1930, **146**, *A*, 30; Halban and Kortüm, *ibid.*, 1934, **170**, *A*, 351; Kortüm, *ibid.*, 1937, **38**, *B*, 1; 1939, **42**, *B*, 39; *Ber.*, 1941, **74**, *B*, 409; Halban and Szigeti, *Helv. Chim. Acta*, 1937, **20**, 746). These authors,

* Photocopies, price 3*s.* each, may be obtained from the General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1, on application quoting the C.S. no.

whose approach is the closest to that used in this Note, and others, did not measure the ionization constants by the method and under the conditions now described.

In a buffered system containing a small amount of acid–base indicator the thermodynamic equilibrium constant K' is given by the equation

$$K' = a_{\mathrm{I},b}a_{\mathrm{A}}/a_{\mathrm{I},a}a_{\mathrm{B}} = Kf_{\mathrm{I},b}f_{\mathrm{A}}/f_{\mathrm{I},a}f_{\mathrm{B}}$$

where the subscripts A, B, and I*a*, I*b* refer to the acid or basic form of the buffer and indicator respectively. On introduction of the Debye–Hückel equation for sufficiently dilute solution, *viz.*, $-\log f_{\mathrm{ion}} = \alpha Z^2\sqrt{\mu}$, it follows that

$$\mathrm{p}K' = \mathrm{p}K - \log f_{\mathrm{I},b}f_{\mathrm{A}}/f_{\mathrm{I},a}f_{\mathrm{B}} = \mathrm{p}K - 2\alpha(Z_{\mathrm{I},a} - Z_{\mathrm{A}})\sqrt{\mu}$$

where $Z_{\mathrm{I},a}$ and Z_{A} are the charges of the indicator acid and the buffer acid respectively. The value of α is given by $\alpha = 1{\cdot}826 \times 10^6/(DT)^{3/2}$, where D is the dielectric constant of the medium.

By plotting the experimental values of pK against the square root of ionic strengths and by calculating the limiting slope by use of $2\alpha(Z_{\mathrm{I},a} - Z_{\mathrm{A}})$ the pK' values are found. Since the indicator acid in the case of nitrophenols is uncharged, the value of $Z_{\mathrm{I},a}$ is equal to zero. Therefore, the values of the expression $2\alpha(Z_{\mathrm{I},a} - Z_{\mathrm{A}})$ depend on the term Z_{A} only, which can be -1, 0, or 1 depending upon whether the buffer acid is of cation, uncharged, or anion type, respectively.

Table 1 shows the calculated values of the slope $2\alpha(Z_{\mathrm{I},a} - Z_{\mathrm{A}})$ as a function of medium and the type of the buffer acid.

TABLE 1. *Calculated values of the slope* $2\alpha(Z_{\mathrm{I},a} - Z_{\mathrm{A}})$.

Solvent		Type of the buffer acid : *		Solvent		Type of the buffer acid : *	
Dioxan, wt. %	D	cation	anion	Dioxan, wt. %	D	cation	anion
0	81·07	−1·020	1·020	70	18·20	− 9·368	9·368
20	62·38	−1·472	1·472	82	9·77	−23·822	23·822
45	39·57	−2·922	2·922				

* Value for uncharged species = zero.

Experimental.—If the dissociation constant of the buffer acid K_{A} is known in the chosen medium, the thermodynamic ionization constant of the dinitrophenol indicators K_{I} can be calculated from the equation $\mathrm{p}K_{\mathrm{I}} = \mathrm{p}K' + \mathrm{p}K_{\mathrm{A}}$. The buffer system acetic acid–sodium acetate (Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, 1950, p. 581) was used for 2 : 5-dinitrophenol, and formic acid–sodium formate (*idem*, *ibid.*) for 2 : 4- and 2 : 6-dinitrophenol.

For the indicators, the ratios between acid and base forms were determined spectrophotometrically at 20°, a Beckman DU Spectrophotometer with water circulation being used. In order to determine the most convenient wave-length for the measurements, full absorption spectra (220—500 mμ) of the sodium dinitrophenoxides were obtained in all the dioxan–water mixtures used. The measurements were made at five different wave-lengths close to the maximum absorption (420—480 mμ) and the ratios found were averaged. The maximum error at a mean pK value was 0·2%. The buffer solutions and 2 ml. of the indicator, all in aqueous solution, were added to the desired amounts of dioxan in a 50-ml. volumetric flask, and the mixtures made up to the mark with water. The solution was then kept in a thermostat at 20° for at least 2 hr. The fraction of indicator in alkaline form was determined by comparing each solution with a corresponding solution of identical ionic strength in which the buffer was replaced by sodium hydroxide.

The values of pK for every system were determined over an ionic strength from about 1×10^{-1} to 5×10^{-4}. Greater ionic strengths than 1×10^{-2} were obtained by addition of lithium chloride or sodium nitrate. In solutions of high dioxan content (70% and 82%) and below an ionic strength of 5×10^{-3} the intermediate yellow colour of the indicator does not appear, and therefore no measurements could be made.

The dinitrophenols were B.D.H. indicator solutions with a concentration of 0·05% for 2 : 4- and 2 : 5-dinitrophenol and of 0·02% for 2 : 6-dinitrophenol. The dioxan was a chemically pure reagent (May and Baker). All other reagents were " Baker's Analyzed c.p.".

Table 2 shows the values of the thermodynamic indicator constants obtained at 20° in different dioxan–water mixtures. The pK values plotted against the mole-fraction of dioxan

TABLE 2. *Thermodynamic indicator constants* (log $pK_{therm.}$) *at* 20°.

Dioxan, wt. %	Dinitrophenol 2 : 4-	2 : 5-	2 : 6-	Dioxan, wt. %	Dinitrophenol 2 : 4-	2 : 5-	2 : 6-
0	4·13	3·75	5·23	70	7·75	7·05	9·45
20	4·75	4·20	5·90	82	9·50	8·80	11·40
45	5·80	5·10	7·15				

give a linear function for 2 : 5- and 2 : 4-dinitrophenol and a very nearly linear function for 2 : 6-dinitrophenol.

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Sulphonium Compounds related to Aryldi-2-halogenoalkylamines.

By J. J. ROBERTS and W. C. J. ROSS.

[Reprint Order No. 5935.]

THE sulphonium dichloride (I) prepared from di-2-chloroethyl sulphide (" mustard gas ") and thiodiglycol $S(CH_2{\cdot}CH_2{\cdot}OH)_2$ possesses a necrotising action approximately one-tenth that of " mustard gas " (Stein, Moore, and Bergmann, *J. Org. Chem.*, **1946**, **11**, 664). There is evidence that the sulphonium dichloride functions as an alkylating agent under mild conditions; for example, with cysteine in a bicarbonate buffer at 37° the diacid (II) is formed. In attempts to obtain biological alkylating agents of greater specificity towards neoplastic tissue (cf. Everett, Roberts, and Ross, *J.*, 1953, 2386) several sulphonium di-iodides related to " aromatic nitrogen mustards " have been prepared. It was hoped that the cationic water-soluble nature of the products would confer special biological activity.

(I) $S[CH_2{\cdot}CH_2{\cdot}\overset{+}{S}(CH_2{\cdot}CH_2{\cdot}OH)_2]_2Cl^-_2$ $S(CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}\underset{NH_2}{CH}{\cdot}CO_2H)_2$ (II)

(III) p-$R{\cdot}C_6H_4{\cdot}N(CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Me_2)_2I^-_2$ β-$C_{10}H_7{\cdot}N(CH_2{\cdot}CHMe{\cdot}\overset{+}{S}Me_2)_2I^-_2$ (IV)

The p-anisidine (III; R = OMe) and p-chloroaniline (III; R = Cl) derivatives were prepared as representative compounds having substituents of opposite polarity. Reaction of the aryldi-2-halogenoethylamine with thiourea gave the corresponding thiuronium salt which on treatment with methyl iodide gave the required sulphonium di-iodides (cf. Walker, *J.*, 1950, 193). These compounds proved to be much less reactive than the parent halogenoethylamines, and so the 2-naphthylamine derivative (IV) and trimethylene-1 : 3-bisdimethylsulphonium di-iodide were also prepared.

All the sulphonium derivatives showed low chemical reactivity when compared with the cytotoxic aryldi-2-halogenoalkylamines, and all were inactive as tumour-growth inhibitors (personal communication from Professor A. Haddow). Significant activity is shown only by bifunctional alkylating agents (Ross, *Adv. Cancer Res.*, 1953, **1**, 397) and hence it was of importance to decide whether the sulphonium compounds suffered fission by water at the *S*-methyl linkage or at the *S*-alkylamine linkage. For the naphthylamine derivative (IV) it was shown that in boiling aqueous acetone the latter occurred, giving *NN*-di-2′-hydroxy-*n*-propyl-2-naphthylamine, whereas on thermal decomposition the former took place with the formation of *NN*-di-2′-methylthiopropyl-2-naphthylamine.

Experimental.— p-*Methoxyphenyliminobis*-(2-*ethylthiuronium chloride*). *NN*-Di-2-chloroethyl-*p*-anisidine (25 g.) (Ross, *J.*, 1949, 183) and thiourea (15 g.) were heated in ethanol (250 ml.) under reflux for 7 hr. After concentration the solution was diluted with ether, giving an oil which solidified when rubbed with dry ether. The *bisthiuronium dichloride* (30 g.) formed prisms, m. p. 204°, from ether–methanol (Found: C, 39·3; H, 6·0; N, 17·4. $C_{13}H_{23}ON_6Cl_3S_2$ requires C, 39·0; H, 5·8; N, 17·5%). Treating the dichloride with an excess of 2N-sodium carbonate gave the free *base*, which formed small prisms, m. p. 84°, from ethyl acetate (Found: C, 47·6; H, 6·4. $C_{13}H_{21}ON_5S_2$ requires C, 47·7; H, 6·5%).

p-*Methoxyphenyliminobis*-(2-*ethyl*-SS-*dimethylsulphonium iodide*). The thiuronium salt (30 g.) was dissolved in warm 2N-sodium hydroxide (400 ml.) and after addition of methyl iodide (10 ml.) to the cooled solution the mixture was shaken for 3 hr. An ethereal extract was

washed with 2N-sodium hydroxide and then water and finally dried (K_2CO_3). On evaporation *NN*-di-2-methylthioethyl-*p*-anisidine (20 g.) which formed a *picrate*, prisms, m. p. 112—114°, from ethanol (Found: C, 45·8; H, 5·1; N, 11·4. $C_{19}H_{24}O_8N_4S_2$ requires C, 45·6; H, 4·8; N, 11·2%) was obtained. A solution of the methylthio-compound (20 g.) and methyl iodide (10 ml.) in methanol (150 ml.) was kept at room temperature for 20 hr. Dilution with dry ether gave an oil which solidified when rubbed with acetone. The *bis-sulphonium di-iodide* formed prisms, m. p. 172—173°, from ethanol (Found: C, 32·4; H, 4·9. $C_{15}H_{27}ONI_2S_2$ requires C, 32·4; H, 4·9 %).

p-*Chlorophenyliminobis*-(2-*ethyl*-SS-*dimethylsulphonium iodide*). Since the corresponding 2-chloroethyl compound was not sufficiently reactive the following were prepared starting from *NN*-di-2-bromoethyl-*p*-chloroaniline: S-p-*Chlorophenyliminobis*-(2-*ethylthiuronium bromide*), prisms, m. p. 194°, from ethanol–chloroform (Found: C, 29·2; H, 4·1. $C_{12}H_{20}N_5ClBr_2S_2$ requires C, 29·2; H, 4·1%), and the corresponding free *base*, prisms, m. p. 96°, from aqueous acetone (Found: C, 43·8; H, 5·3. $C_{12}H_{15}N_5ClS_2$ requires C, 43·4; H, 5·5%); *NN*-di-2-methylthioethyl-*p*-chloroaniline, characterised as its *picrate*, prisms, m. p. 114—116°, from ethanol (Found: C, 42·8; H, 4·4. $C_{18}H_{21}O_7N_4ClS_2$ requires C, 42·8; H, 4·2%); S-p-*chlorophenyliminobis*-(2-*ethyl*-SS-*dimethylsulphonium iodide*), prisms, m. p. 128·5—131°, from ether–methanol (Found: C, 29·8; H, 4·5; N, 2·6. $C_{14}H_{24}NClI_2S_2$ requires C, 30·0; H, 4·3; N, 2·5%), and the corresponding p-*chloroaniline dipicrate*, prisms, m. p. 159—160°, from water (Found: C, 40·4; H, 3·7. $C_{26}H_{28}O_{14}N_7ClS_2$ requires C, 41·0; H, 3·7%).

β-*Naphthyliminobis*-[2-(1-*methylethyl*)-SS-*dimethylsulphonium iodide*]. *NN*-Di-2-chloropropyl-β-naphthylamine (Everett and Ross, *J.*, 1949, 1972) was converted into NN-*di*-2-*methylthiopropyl*-β-*naphthylamine picrate*, prisms, m. p. 112°, from ethanol (Found: C, 52·8; H, 5·4; N, 10·1. $C_{24}H_{28}O_7N_4S_2$ requires C, 52·5; H, 5·1; N, 10·2%), and thence into the *bis-sulphonium iodide*, a hygroscopic solid, m. p. 50—60° (decomp.) (Found: C, 39·3; H, 5·5; N, 2·2; S, 10·1. $C_{20}H_{31}NI_2S_2$ requires C, 39·8; H, 5·2; N, 2·3; S, 10·6%).

A solution of the di-iodide (400 mg.) in 50% aqueous acetone (100 ml.) was heated under reflux for 50 hr. The concentrated solution was extracted with ether, giving an oil which formed a *picrate*, prisms (from benzene), m. p. 164—168°, undepressed on admixture with the picrate of *NN*-di-2-hydroxypropyl-β-naphthylamine (Found: C, 53·7; H, 5·2; N, 11·3. $C_{22}H_{24}O_9N_4$ requires C, 54·1; H, 5·0; N, 11·5%).

The residue obtained when the di-iodide was heated for some time on a water-bath formed a picrate, m. p. 119°, undepressed on admixture with *NN*-di-2-methylthiopropyl-β-naphthylamine picrate.

Trimethylenebis(*dimethylsulphonium iodide*). A mixture of 1 : 3-bismethylthiopropane (9 g.) (Mathias, *Bol. Fac. Filosofia, Cienc., Letras, Univ. Sao Paulo Quimica*, 1942, No. 1, 75; *Chem. Abs.*, 1946, **40**, 2793), methyl iodide (9 ml.), and methyl alcohol (10 ml.) was kept at room temperature for 24 hr. The *bis-sulphonium iodide* which separated from the solution formed prisms, m. p. 155° (decomp.), from methanol (Found: C, 20·4; H, 4·6. $C_7H_{16}I_2S_2$ requires C, 20·0; H, 4·3%).

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2-*Alkylthio*-4 : 5-*dihydroglyoxalinium Salts*.

By Walter Wilson.

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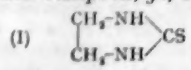
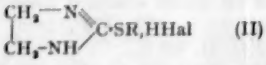
4 : 5-Dihydroglyoxalines are readily prepared by treating tetrahydro-2-thioglyoxaline (I) with alkyl halides, which give the *S*-alkyl compounds (as II) (Schacht, *Arch. Pharm.*, 1897, **235**, 445, and many later papers; cf. Knott and Morgan, U.S.P. 2,514,650; Aspinall and Bianco, *J. Amer. Chem. Soc.*, 1951, **73**, 602; Easton, Hlynsky, and Foster, *ibid.*, p. 3507; Baer and Lockwood, *ibid.*, 1954, **76**, 1162). The base formed from tetrahydro-2-thioglyoxaline, formaldehyde, and piperidine gives a dihydrochloride (Jones and Turner, *J.*, 1950, 1515), and is therefore probably the 2-substituted compound (as II; R =

$CH_2{\cdot}NC_5H_{10}$). We have prepared a series of 2-alkylthio-4 : 5-dihydroglyoxalinium salts (II) and corresponding bis-compounds (see Table) from halogen compounds. These salts and the corresponding picrates and bases may be useful for characterisation of alkyl halides and dihalides (cf. the *S*-alkylthiuronium compounds; Brown and Campbell, *J.*, 1937, 1699; Levy and Campbell, *J.*, 1939, 1442).



(I)



(II)

The pK_a values (see Table) fall in the range 8·4—9·6 (Baer and Lockwood, *loc. cit.*, give 9·0 for 2-*n*-butylthiodihydroglyoxaline). The strength of the second basic group in the bis-compounds shows the expected depression, less so as the distance between the basic centres increases. 2-Alkylthiodihydroglyoxalines are much weaker bases than guanidines (pK_a 13·4—13·7 in water; Albert, Goldacre, and Philips, *J.*, 1948, 2240; Angyal and Warburton, *J.*, 1951, 2492), and are appreciably weaker than closely related amidines or dihydroglyoxalines [acetamidine, pK_a 12·52; benzamidine 11·6 in water, Albert, Goldacre, and Philips, *loc. cit.*; 2-diphenylyldihydroglyoxaline, pK_a 9·29 in 50% ethanol, Cymerman-Craig, Parker, and Woodhouse, *J.*, 1953, 3050; 2-diphenylmethyldihydroglyoxaline pK_a 9·64 in 50% ethanol (present work)].

2-Benzylthiodihydroglyoxaline is stable, and with hot alkali forms toluene-ω-thiol only slowly. In contrast, *S*-benzyl*iso*thiourea decomposes when warmed, and instantaneously gives toluene-ω-thiol with hot 2N-alkali; *N*- and *NN'*-substituted *S*-alkyl*iso*thioureas behave similarly, affording thiols and cyanamides or carbodi-imides and their further transformation products (Arndt, *Annalen*, 1911, **384**, 331; *Ber.*, 1921, **54**, 2236; Rhône-Poulenc, Brit. Pat., 649,634; *Chem. Abs.*, 1951, **45**, 8040; Will *et al.*, *Ber.*, 1882, **15**, 338, 1312; Werner, *J.*, 1890, **303**). 2-Alkylthiodihydroglyoxalines could not readily undergo elimination reactions of this type, because the product would be a highly strained (and unknown) cyclic carbodi-imide; the relatively slow reaction of 2-alkylthiodihydroglyoxalines with alkalis is possibly hydrolytic.

The reaction of *S*-alkyl*iso*thiuronium and 2-alkylthiodihydroglyoxalinium salts with strongly basic amines (Aspinall and Bianco, *loc. cit.*; Philips and Clarke, *J. Amer. Chem. Soc.*, 1923, **45**, 1755) does not occur with the amine hydrochlorides; the strong acid probably reduces the nucleophilic activity of the amine (cf. Lythgoe, *Quart. Rev.*, 1949, **3**, 197); acetic acid does not have this effect.

In tetrahydrothioglyoxaline itself, the sulphur is less labile than in thiourea, as shown by reactions with heavy-metal compounds (Experimental section). With mercuric oxide it affords tetrahydro-2-oxoglyoxaline (Klut, *Arch. Pharm.*, 1902, **240**, 677); substituted thioureas generally afford cyanamides or carbodi-imides, in addition to ureas, with lead or mercuric oxides (cf., *e.g.*, Khorana, *Chem. Rev.*, 1953, **53**, 145; Lecher and Gubernator, *J. Amer. Chem. Soc.*, 1953, **75**, 1087).

Experimental.—*SS'-Decamethylenebis-(2-thio-4 : 5-dihydroglyoxalinium bromide).* Tetrahydro-2-thioglyoxaline (*Org. Synth.*, 1946, **26**, 34) (4·08 g.), propanol (50 c.c.), and 1 : 10-dibromodecane (6·0 g.) were refluxed for 6 hr., then cooled, and a little ether was added. The product (7·6 g.; m. p. 173—175°) was recrystallised from ethanol, giving the *dibromide*, m. p. 174—176° (see Table). The other compounds listed were prepared similarly, being crystallised from ethanol, ethanol–ether, or aqueous ethanol. The pK_a values were determined electrometrically in 50% aqueous ethanol at 20—25° by titration of the salts with potassium hydroxide solution. Results were not obtained in some cases because of difficult solubilities.

Reactions of 2-benzylthio-4 : 5-dihydroglyoxalinium chloride. The chloride was refluxed with methylammonium or ammonium chloride in water; no thiol was formed. After addition of sodium acetate or hydroxide, toluene-ω-thiol was rapidly formed. The chloride also rapidly gave the thiol when warmed with ammonia, ammonium acetate, or methylamine solution, but only slowly with trimethylamine or sodium acetate solution. *S*-Benzylthiuronium chloride behaved similarly. *S*-Methyl compounds were less reactive than *S*-benzyl compounds in most reactions.

Reactions of tetrahydro-2-thioglyoxaline. Tschugaeff's reagent (Ph_3CCl_2) for CS groups (*Ber.*, 1902, **35**, 2483) gave an intense blue colour, changing to green, then brown. Similar colours were obtained with thiourea. Hot aqueous silver nitrate gave a slight turbidity with the glyoxaline,

2-*Alkylthio*-4 : 5-*dihydroglyoxalinium* halides and SS'-*alkylenebis*-(2-*thio*-4 : 5-*dihydroglyoxalinium*) *dihalides.*

Halide used	Yield (%)	M. p.	pK_{a_1}	pK_{a_2}	Formula	Found C	Found H	Calc. C	Calc. H
Methyl iodide	98	140—141° [1]	8·9	—	$C_4H_8N_2S,HI$	20·0	4·0	19·7	3·7
n-Hexyl bromide	90 [2]	54—55 [2]	—	—	*$C_9H_{18}N_2S$ (base)	58·0	9·7	58·1	9·7
n-Hexadecyl iodide	41	83·5—84 [3]	—	—	*$C_{19}H_{38}N_2S,HI$	50·7	8·8	50·3	8·65
1 : 2-Dibromoethane ...	90	275—276 [4] †	8·97	6·15	*$C_6H_{14}N_4S_2,2HBr$	24·6	4·2	24·5	4·1
1 : 3-Dibromopropane ...	87	221—222 [5]	9·57	8·03	$C_9H_{18}N_4S_2,2HBr$	26·95	4·5	26·6	4·5
1 : 4-Dibromobutane ...	93	205	9·33	8·09	*$C_{10}H_{18}N_4S_2,2HBr$	28·1	4·7	28·6	4·75
1 : 10-Dibromodecane ...	76	174—176	—	—	*$C_{16}H_{30}N_4S_2,2HBr$	38·1	6·5	38·1	6·35
2-Diethylaminoethyl chloride hydrochloride	77	172 [6]	—	—	$C_9H_{19}N_2S,2HCl$	39·75	7·8	39·4	7·7
Benzyl chloride	88	169—171 [7]	8·43	—	$C_{10}H_{12}N_2S,HCl$	52·5	5·7	52·5	5·7
p-Nitrobenzyl bromide	85	150—151 [8] 174—176	—	—	*$C_{10}H_{11}O_2N_3S,HBr$	N, 12·6		N, 13·2	
o-Xylylene dibromide [9]	86	200—201	8·88	7·53	*$C_{14}H_{18}N_4S_2,2HBr$	35·1	4·75	35·9	4·3
4 : 4'-Bischloromethyldiphenylmethane [10] ...	88	219	—	—	*$C_{31}H_{34}N_4S_2,2HCl$	53·85	6·15	53·7	5·6

* New compound. † With decomp.

[1] Free base, m. p. 100—102°, very soluble in water, extracted by ether; *picrate*, m. p. 177·5—178°, bright yellow prisms from ethanol (Found : C, 34·75; H, 3·3. $C_4H_8N_2S,C_6H_3O_7N_3$ requires C, 34·8; H, 3·2%). For the iodide Schacht (*loc. cit.*) gives m. p. 145° and Aspinall and Bianco (*loc. cit.*), m. p. 142°. [2] Hydrobromide not crystalline; product isolated as base, and recryst. from light petroleum (b. p. 60—80°). [3] Hydrobromide probably has m. p. 105° (Imazu and Takada, quoted by *Chem. Abs.*, 1950, **44**, 7775). [4] Schacht, and Knott and Morgan (*locc. cit.*), give no m. p.; Knott and Morgan give m. p. 203° for the base. [5] Knott and Morgan (*loc. cit.*) give m. p. 224°. [6] Polymorphic change at *ca.* 140°. [7] Polymorphic change at *ca.* 146°; Forrest and Walker (*J.*, 1949, 2002) give m. p. 145—145·5°; Aspinall and Bianco (*loc. cit.*) give m. p. 172° (cf. Baer and Lockwood, *loc. cit.*). The base was stable and formed large tablets or needles [from light petroleum (b. p. 60—80°)], m. p. 69° [Found : C, 62·45; H, 6·45%; *M* (Rast), 172. Calc. for $C_{10}H_{12}N_2S$: C, 62·45; H, 6·3%; *M*, 192]; Easton, Hlynsky, and Foster (*loc. cit.*) give m. p. 68—70°. *Picrate*, needles, m. p. 162°, from ethanol (Found : N, 16·9. $C_{10}H_{12}N_2S,C_6H_3O_7N_3$ requires N, 16·1%). [8] Base, m. p. 158°, hydrochloride, m. p. 191° (Easton, Hlynsky, and Foster, *loc. cit.*). [9] Perkin, *J.*, 1888, **53**, 5; Atkinson and Thorpe, *J.*, 1907, **91**, 1687. [10] Reichstein and Oppenauer, *Helv. Chim. Acta*, 1933, **16**, 1373.

and a black precipitate with thiourea. With ammoniacal silver nitrate, the precipitates were white and black respectively. Warm aqueous sodium plumbite gave a black precipitate with thiourea, but none with the glyoxaline.

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Vapour Pressures of Some Unsaturated Hydrocarbons containing Six Carbon Atoms.

By G. A. McD. CUMMINGS and E. McLAUGHLIN.

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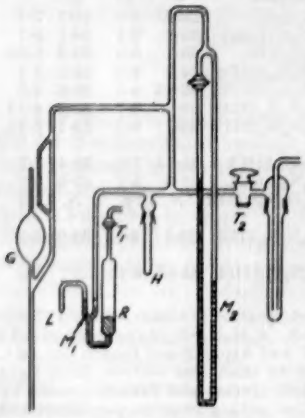
THE vapour pressures of hexa-1 : 5-diene, 2 : 3-dimethylbuta-1 : 3-diene, and 2 : 3-dimethylbut-2-ene were determined for the range 0—40°, to provide data for the evaluation of diffusion coefficients (Cummings, McLaughlin, and Ubbelohde, to be published). Heats of vaporisation and molar entropies of vaporisation at the boiling point were derived from these data.

Materials.—Hexa-1 : 5-diene (b. p. 59·2° ± 0·1°/750·8 mm., n_D^{20} 1·4042), 2 : 3-dimethylbuta-1 : 3-diene (b. p. 68·4° ± 0·1°/757·0 mm., n_D^{20} 1·4391), and 2 : 3-dimethylbut-2-ene (b. p. 74·1° ± 0·1°/781·0 mm., n_D^{20} 1·4122) were prepared and purified as previously described (Cummings, McCoubrey, and Ubbelohde, *J.*, 1952, 2725), special care being taken to prevent the formation of peroxides (Howard *et al.*, *J. Res. Nat. Bur. Stand.*, 1947, **38**, 365).

Apparatus and Technique.—The vapour pressures were measured by the static method in the apparatus illustrated, which was made of 1-cm. bore Pyrex tubing and could be evacuated

by a two-stage mercury diffusion pump backed by a rotary pump. Before each run, the limb L was baked out under vacuum, a coal-gas flame being used. A sample of the hydrocarbon was introduced into the tube H where it was degassed by repeated melting and freezing under vacuum. It was then allowed to distil from H and the middle fraction was collected in L and frozen in liquid air, and the whole system pumped out to better than 10^{-3} mm., as read on the McLeod gauge G. A slight amount of air was allowed to leak into the reservoir R through a capillary leak and tap T_1, thus forcing the mercury in R to rise in the manometer M_1. Subsequently the manometer M_1, the reservoir R, and the limb L were immersed in a water thermostat accurate to $\pm 0{\cdot}02°$. Temperatures were read to $\pm 0{\cdot}02°$ on a mercury-in-glass (N.P.L.) thermometer, 0—40°.



The liquid in L was allowed 1—2 hr. to reach temperature equilibrium, the exact time being determined by the reproducibility of the subsequent readings. The mercury in the limbs of the manometer M_1 was then levelled by admitting air through a capillary leak, or by pumping out, *via* T_1 or T_2. The small difference Δh_1 in level in the manometer M_1 was read on a Pye cathetometer to $\pm 0{\cdot}05$ mm. The difference in level dh_2 of the manometer M_2 was also read to $\pm 0{\cdot}05$ mm., and Δh_1 and Δh_2 summed to give the required vapour pressure at the temperature of measurement. As the highest temperature of measurement was approximately 40°, approximate levelling of the mercury column in M_1 rendered a temperature correction to Δh_1 unnecessary, as any such correction was well within the limits of accuracy of the temperature control. Readings were taken as the temperature of the thermostat was raised and as it was lowered, the latter readings being discontinued when condensation of the hydrocarbon distorted the mercury meniscus in M_1. The average precision was $\pm 0{\cdot}2$ mm. Results are given in Table 1.

TABLE 1.

2 : 3-Dimethylbuta-1 : 3-diene				2 : 3-Dimethylbut-2-ene				Hexa-1 : 5-diene			
Temp.	V. p., mm.	Temp.	V. p., mm.	Temp.	V. p., mm.	Temp.	V. p., mm.	Temp.	V. p., mm.	Temp.	V. p., mm.
0·04°	46·0	17·24°	106·8	12·98°	78·3	24·89°	132·2	0·04°	71·9	16·52°	156·5
12·00	83·7	19·86	120·4	13·99	81·9	29·83	162·8	12·96	133·3	17·83	164·9
13·46	89·6	25·74	156·2	15·94	89·4	34·93	199·8	13·90	138·9	31·00	282·6
15·42	98·4	31·35	197·8	16·99	93·6	39·88	242·4	14·83	144·8	38·22	370·3
16·96	105·9	68·4	757·0	19·04	102·6	74·1	781·0	15·64	149·9	59·2	750·8

The data were extrapolated to the boiling points and the vapour pressure–temperature curves fitted to the logarithmic equation $\log_{10} p = A - B/(t + C)$ (cf. Thomson, *Chem. Rev.*, 1946, **38**, 1) where p is the pressure in mm. and t the temperature. Table 2 gives the constants A, B, and C for the three compounds, and also the heats of vaporisation and molar entropies of vaporisation, at saturation pressure, at the normal boiling point. These values, calculated from the vapour pressure data, were obtained from the equation

TABLE 2.

Compound	A	B	C	$\Delta H_{vap.}$ (cal./mole)	$\Delta S_{vap.}$ (cal./deg. mole)
Hexa-1 : 5-diene	6·6119	1032	217·0	6830	20·5
2 : 3-Dimethylbuta-1 : 3-diene	7·2017	1346	243·0	7410	21·7
2 : 3-Dimethylbut-2-ene	7·2550	1430	253·7	7340	21·2

$$\Delta S_{vap.} = \frac{\Delta H_{vap.}}{T} = \frac{2{\cdot}303RTB}{(t+C)^2} \cdot \frac{P\Delta V}{RT}$$

where T is the boiling point (°K) at 760 mm. Perfect gas laws were assumed and $P\Delta V/(RT)$ was taken as unity.

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